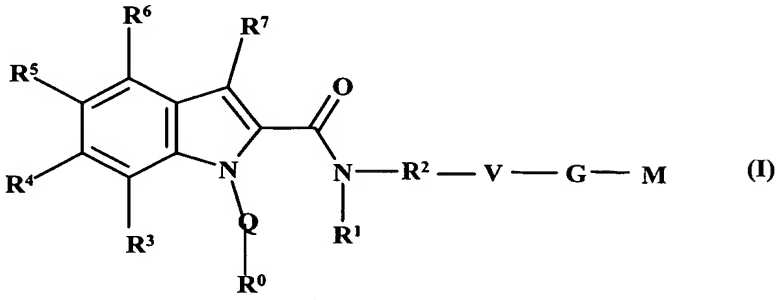
Indole Derivatives as Factor Xa Inhibitors

Field of the Invention

The present invention relates to compounds of the formula I,



in which R^0 ; R^1 ; R^2 ; R^3 ; R^4 ; R^5 ; R^6 ; R^7 ; Q; V, G and M have the meanings indicated below. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

Background of the Invention

Normal haemeostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs (EP-A-987274). Many significant disease states are related to abnormal haemeostasis. For example,

local thrombus formation due to rupture of atheroslerotic plaque is a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

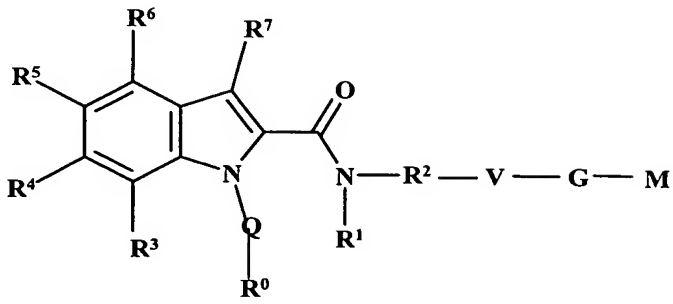
There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation. It is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor Xa and/or factor VIIa activity. It is now believed that inhibitors of factor Xa carry a lower bleeding risk than thrombin inhibitors (A. E. P. Adang & J. B. M. Rewinkel, Drugs of the Future 2000, 25, 369-383). Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do not cause unwanted side effects have been described, for example, in WO-A-95/29189.
However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous properties, for instance stability in plasma and liver and selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors, which are effective and have the above advantages as well.

Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example discloses compounds containing a tripeptide unit, which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for further low molecular weight factor VIIa inhibitory blood clotting inhibitors. WO-A-99/33800 discloses indole derivatives, which inhibit factor Xa activity.

The present invention satisfies the above needs by providing novel compounds of the formula I, which exhibit better factor Xa and/or factor VIIa inhibitory activity and are favorable agents with high bioavailability.

Summary of the Invention

Thus, the present invention relates to compounds of the formula I,



(I)

wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a monocyclic or bicyclic 4- to 15-membered heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$,

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or –O-(C_1-C_8)-alkyl,

9) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10) –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11) -SO_2-CH_3 or

12) –SO_2-CF_3,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl or a monocyclic or bicyclic 4- to 15-membered heterocyclyl,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -(C_1-C_6)-alkylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-,

-$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-,

-$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-,

-(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-,

-(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or

–(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R^{15}, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1 and R^7 together with the atoms to which they are bonded can form a 6- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

R^1-N-R^2-V can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a 3- to 7-membered cyclic residue, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic

residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

2) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$,

$-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) $-(C_3-C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-C(O)-R^{11}$,

12) $-C(O)-O-R^{11}$,

13) $-C(O)-N(R^{11})-R^{12}$,

14) $-N(R^{11})-R^{12}$,

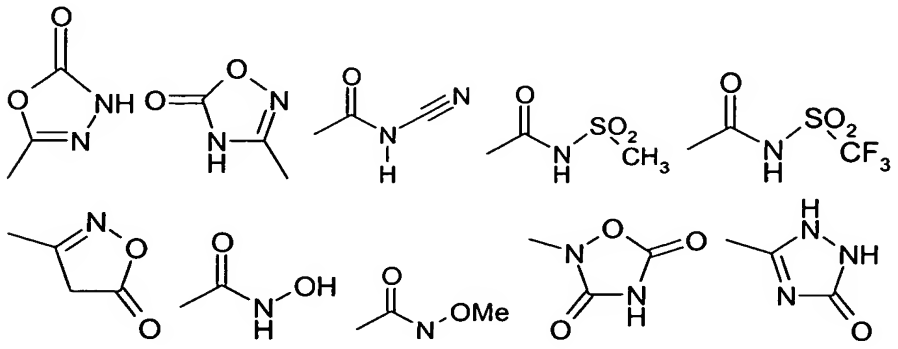
15) $-NR^{10}-SO_2-R^{10}$,

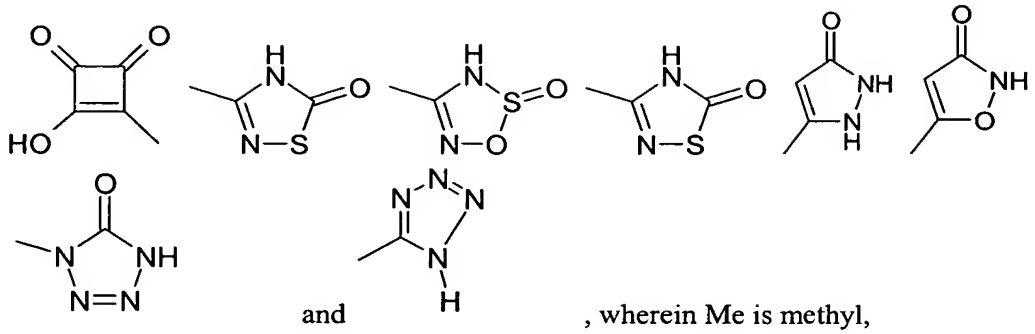
16) $-S-R^{10}$,

17) -C(O)-O-C(R15, R16)-O-C(O)-R17,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

20) a residue from the following list





and , wherein Me is methyl,

20) -(C_1-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

21) -(C_1-C_4)-alkylene-C(O)-R^{11},

22) -(C_1-C_4)-alkylene-C(O)-O-R^{11},

23) -(C_1-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

24) -(C_1-C_4)-alkylene-N(R^{11})-R^{12},

25) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

26) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

27) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

28) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

29) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

30) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

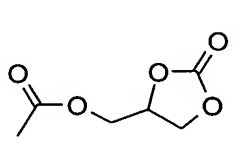
31) -(C_0-C_4)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_4)-alkyl,

32) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R13,

33) -(C_0-C_4)-alkylene-N(R^{11})-R13,

34) =O,

35) the following residues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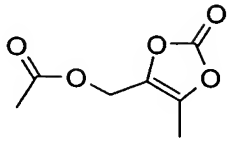

or

36) if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 5- or 6- membered ring, which is unsubstituted or substituted one, two, three or four times by R13,

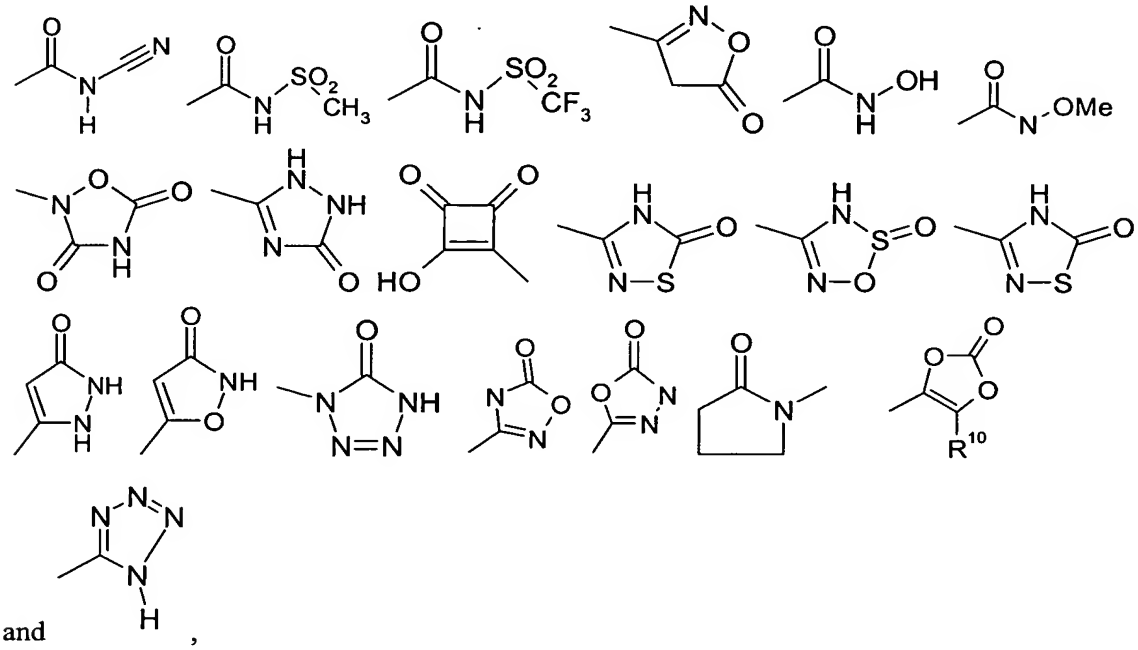
R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,
2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,
4) -SO_t-R^{10}, wherein t is 1 or 2,
5) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,
6) -(C_1-C_3)-perfluoroalkyl,
7) -O-R^{17}, or
8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_3-C_8)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_u$-R^{10}, wherein u is 1 or 2, -S-R^{10}, -SO_r-R^{10}, wherein r is 1 or 2, -S(O)$_v$-N(R^{10})-R^{20}, wherein v is 1 or 2, -C(O)-R^{10},
-(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-,

-O-CF_3, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -(C_1-C_3)-perfluoroalkyl, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, or a residue from the following list



and ,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl,

-(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 20) to 36), or

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered monocyclic heterocyclic ring, which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen;

wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-OH or -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, or

provided that R13 is -(C_0-C_3)-alkylene-O-R^{10}, or

provided that R11 is hydrogen atom and R12 is -O-R17,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2) The present invention also relates to compounds of the formula I, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a monocyclic or bicyclic 4- to 15-membered heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$,

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or –O-(C_1-C_8)-alkyl,

9) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or

10) –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11) -SO_2-CH_3 or

12) –SO_2-CF_3,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl or a monocyclic or bicyclic 4- to 15-membered heterocyclyl,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, -(C_1-C_6)-alkylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-,

-$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-,

-$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-,

-(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-,

-(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or –(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1 and R^7 together with the atoms to which they are bonded can form a 6- to 8-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

R^1-N-R^2-V can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, $-NO_2$, -C(O)-OH, -CN, $-NH_2$, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a 3- to 7-membered cyclic residue, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

2) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$,

$-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) $-(C_4-C_{15})$-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) $-(C_3-C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -O-R19, wherein R19 is

   a) hydrogen atom,

   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

   d) $-CF_3$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-C(O)-R^{11}$,

12) $-C(O)-O-R^{11}$,

13) $-C(O)-N(R^{11})-R^{12}$,

14) $-N(R^{11})-R^{12}$,

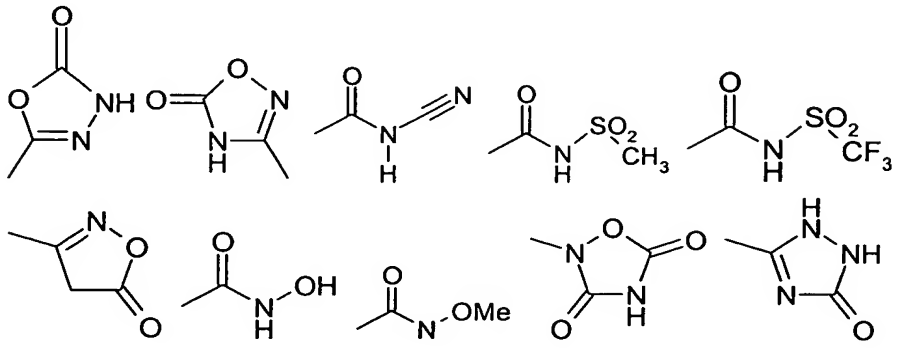
15) $-NR^{10}-SO_2-R^{10}$,

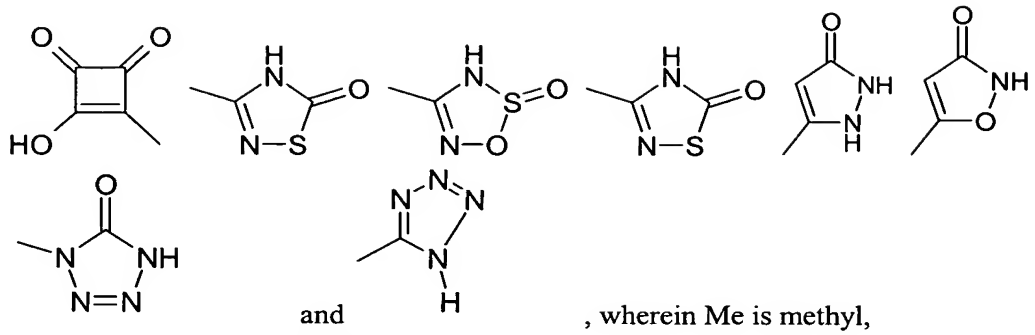
16) $-S-R^{10}$,

17) -C(O)-O-C(R15, R16)-O-C(O)-R17,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

19) a residue from the following list





and , wherein Me is methyl,

20) -(C_1-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

21) -(C_1-C_4)-alkylene-C(O)-R^{11},

22) -(C_1-C_4)-alkylene-C(O)-O-R^{11},

23) -(C_1-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

24) -(C_1-C_4)-alkylene-N(R^{11})-R^{12},

25) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

26) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

27) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

28) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

29) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

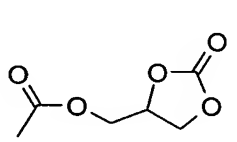
30) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

31) -(C_0-C_4)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_4)-alkyl,

32) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R13,

33) -(C_0-C_4)-alkylene-N(R^{11})-R13,

34) the following residues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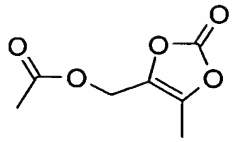

or

35) if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 5- or 6- membered ring, which is unsubstituted or substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

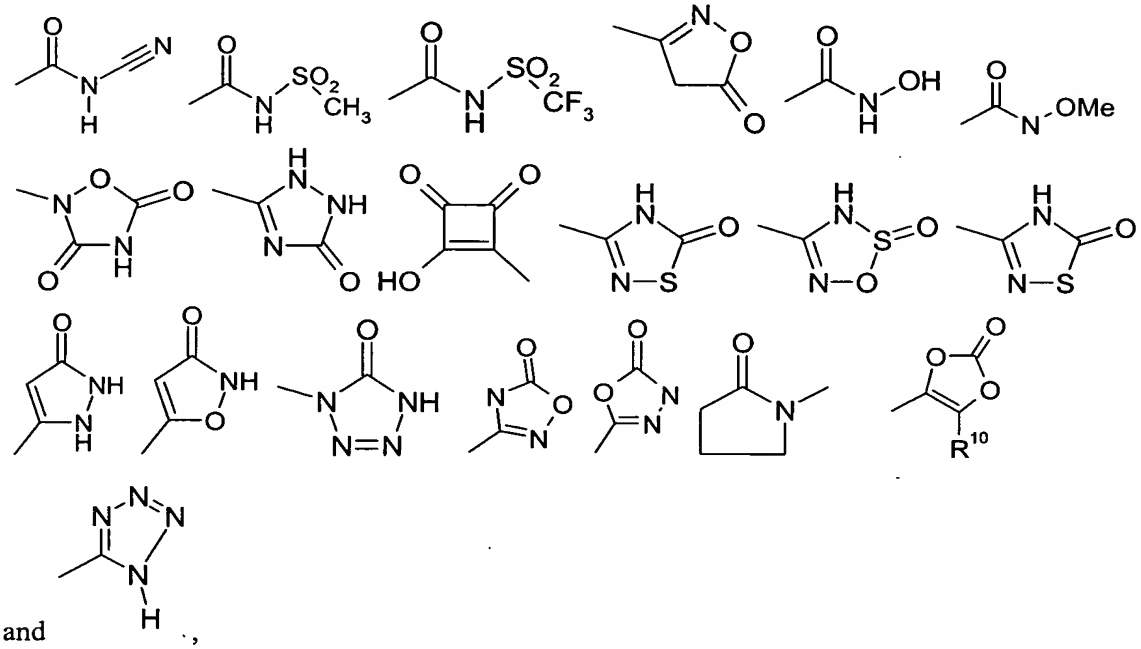
1) hydrogen atom,
2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,
4) -SO_t-R^{10}, wherein t is 1 or 2,
5) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,
6) -(C_1-C_3)-perfluoroalkyl,
7) -O-R^{17}, or
8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20},

-(C_3-C_8)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-$(CH_3)_3$, -N(R^{10})-S(O)$_u$-R^{10}, wherein u is 1 or 2, -S-R^{10}, -SO_r-R^{10}, wherein r is 1 or 2, -S(O)$_v$-N(R^{10})-R^{20}, wherein v is 1 or 2, -C(O)-R^{10}, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-,

-O-CF_3, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -(C_1-C_3)-perfluoroalkyl, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, or a residue from the following list



and ,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl,

-(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 20) to 35),

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered ring out of the group selected from azetidine, 2,3-dihydro-azete, 1,2-dihydro-azete, azete, [1,3]diazetidine, 1,2-dihydro-[1,3]diazete, [1,3]diazete, [1,2,3]triazetidine, 1,2-dihydro-[1,2,3]triazete, [1,2,3]triazete, 1,4-dihydro-[1,2,3]triazete, [1,3]oxazetidine, 2H-[1,3]oxazete,

[1,2]oxazetidine, 4H-[1,2]oxazete, 2H-[1,2]oxazete, [1,3]thiazetidine, 2H-[1,3]thiazete, [1,3]thiazete, [1,2]thiazetidine, 4H-[1,2]thiazete, 2H-[1,2]thiazete or [1,2]thiazete or azocane, azocane-2-one, [1,5]diazocane , [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, [1,4]oxazepane, [1,3]oxazepane, [1,3]thiazepane, [1,4]oxazocane, [1,3]oxazocan-2-one, 5,6,7,8-tetrahydro-1H-azocin-2-one, thiacepane, [1,5]thiazocane or [1,4]thiazocane, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_4)-alkyl-O-(C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, -(C_1-C_4)-alkyl-OH or -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl, or

provided that R13 is -(C_0-C_3)-alkylene-O-R^{10} , or

provided that R11 is hydrogen atom and R12 is -O-R17,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3) Thus, the present invention relates to compounds of the formula I, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl, wherein heterocyclyl is selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl,

octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and

which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl,

tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is
1) halogen,
2) $-NO_2$,
3) -CN,
4) $-C(O)-NH_2$,
5) -OH,
6) $-NH_2$,
7) $-O-CF_3$,
8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,
9) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
10) $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,
11) $-SO_2-CH_3$ or
12) $-SO_2-CF_3$,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl or a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein aryl and heterocyclyl are as defined above,

Q is a direct bond, $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, $-(C_1-C_6)$-alkylene, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$-,

$-(CH_2)_m-S-(CH_2)_n$-, $-(CH_2)_m-C(O)-(CH_2)_n$-, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$-,

$-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$,

$-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$, $-(C_2-C_3)$-alkylene-O-(C_0-C_3)-alkylene-, $-(C_2-C_3)$-alkylene-S(O)-,

$-(C_2-C_3)$-alkylene-$S(O)_2-$, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$, $-(C_2-C_3)$-alkylene-$S(O)_2$-NH-$(R^{10})-$,

$-(C_2-C_3)$-alkylene-$N(R^{10})-$ or $-(C_0-C_3)$-alkylene-C(O)-O- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by $-(CH_2)_m-$ or $-(CH_2)_n-$ are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or –OH; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or –OH;

R^1 is a hydrogen atom, $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; $-(C_1-C_3)$-alkylene-C(O)-NH-R^0, $-(C_1-C_3)$-alkylene-C(O)-O-R15, an aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above;
a monocyclic or bicyclic 4- to 15-membered heterocyclyl,which is as defined above;
$-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-S(O)-(C_1-C_4)-alkyl,
$-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2-N(R^{4'})-R^{5'}$,
$-(C_1-C_3)$-alkylene-O-(C_1-C_4)-alkyl, $-(C_0-C_3)$-alkylene-(C_3-C_8)-cycloalkyl, or
$-(C_0-C_3)$-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-

triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1 and R^7 together with the atoms to which they are bonded can form a 6- to 8-membered cyclic residue selected out of the group azocane, azocane-2-one, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazine, [1,4]dioxocane, dioxole, ketopiperazine, morpholine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, [oxocane, oxocan-2-one, piperazine, piperidine, pyran, pyrazine, pyridazine, pyrimidine or 5,6,7,8-tetrahydro-1H-azocin-2-one, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

R^1-N-R^2-V can form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl,

-C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R14,

2) a heterocyclyl out of the group acridinyl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxazolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$,
$-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) -(C_6-C_{14})-aryl, wherein aryl is as defined above and wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) -(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

d) -CF_3,

7) -NO_2,

8) -CN,

9) -SO_s-R^{11}, wherein s is 1 or 2,

10) -SO_t-N(R^{11})-R^{12}, wherein t is 1 or 2,

11) -C(O)-R^{11},

12) -C(O)-O-R^{11},

13) -C(O)-N(R^{11})-R^{12},

14) -N(R^{11})-R^{12},

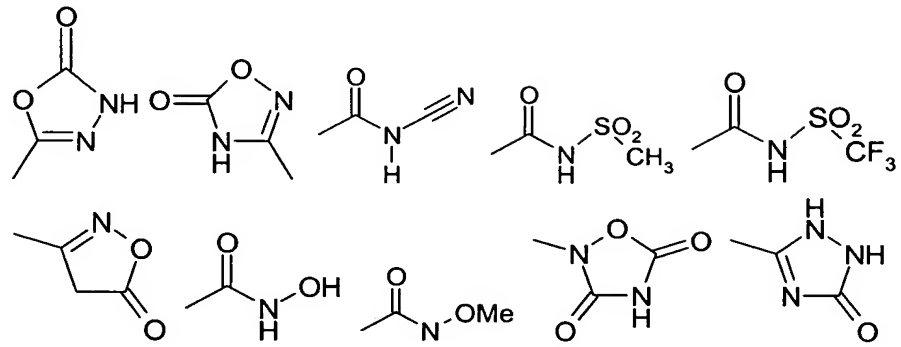
15) -NR^{10}-SO_2-R^{10},

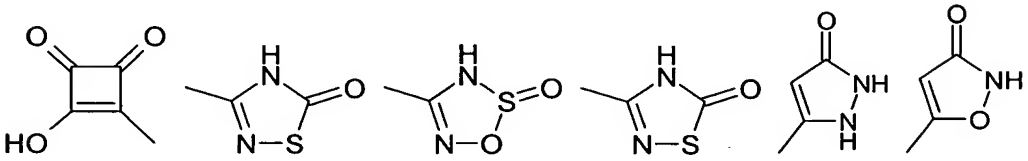
16) -S-R^{10},

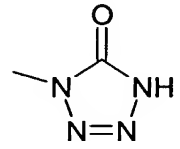
17) -C(O)-O-C(R15, R16)-O-C(O)-R17,

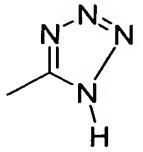
18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

19) a residue from the following list







and  , wherein Me is methyl,

20) -(C_1-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) -CF_3, or

e) $-CHF_2$,

21) $-(C_1-C_4)$-alkylene-C(O)-R^{11},

22) $-(C_1-C_4)$-alkylene-C(O)-O-R^{11},

23) $-(C_1-C_4)$-alkylene-C(O)-N(R^{11})-R^{12},

24) $-(C_1-C_4)$-alkylene-N(R^{11})-R^{12},

25) $-(C_0-C_2)$-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

26) $-(C_0-C_2)$-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

27) $-(C_0-C_4)$-alkylene-(C_6-C_{14})-aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by R13,

28) $-(C_0-C_4)$-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

29) $-(C_0-C_4)$-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

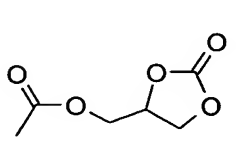
30) $-(C_0-C_4)$-alkylene-het, wherein het is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

31) $-(C_0-C_3)$-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_3)-alkyl,

32) $-(C_0-C_4)$-alkylene-C(O)-N(R^{11})-R13,

33) $-(C_0-C_4)$-alkylene-N(R^{11})-R13,

34) the following residues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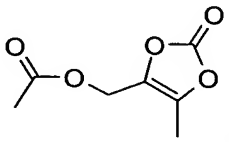

or

35) if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) $-(C_0-C_6)$-alkyl-(C_3-C_8)-cycloalkyl,

4) $-SO_t-R^{10}$, wherein t is 1 or 2,

5) $-(C_0-C_6)$-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

6) $-(C_1-C_3)$-perfluoroalkyl,

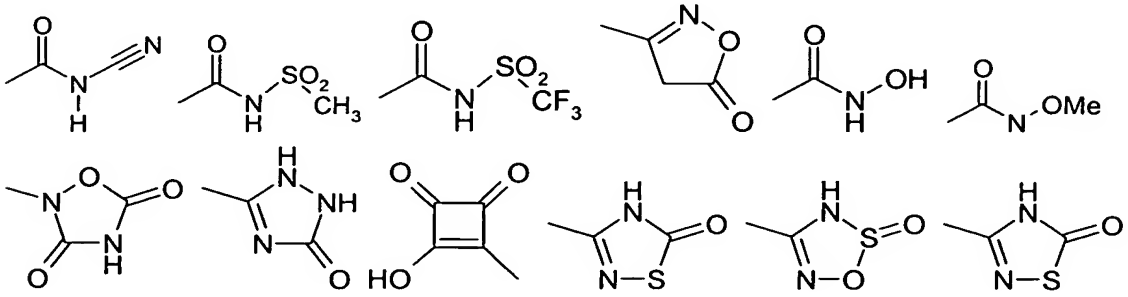
7) $-O-R^{17}$, or

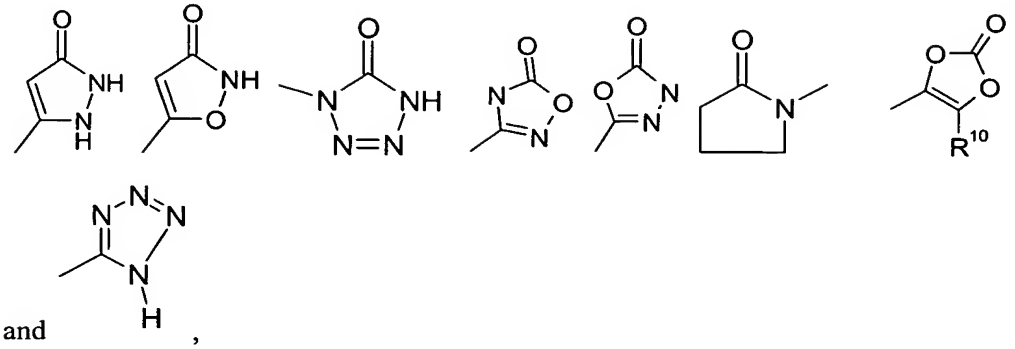
8) $-(C_0-C_6)$-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl are as defined above and are independently from one another unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring out of the group azepine, azetidine, dioxazole, dioxazine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$,

$-(C_3-C_8)$-cycloalkyl, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, wherein u is 1 or 2, $-S-R^{10}$, $-SO_r-R^{10}$, wherein r is 1 or 2, $-S(O)_v-N(R^{10})-R^{20}$, wherein v is 1 or 2, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, $-(C_1-C_3)$-perfluoroalkyl, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list





and ,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl;

-(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 20) to 35), or

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered ring out of the group selected from azetidine, 2,3-dihydro-azete, 1,2-dihydro-azete, azete, [1,3]diazetidine, 1,2-dihydro-[1,3]diazete, [1,3]diazete, [1,2,3]triazetidine, 1,2-dihydro-[1,2,3]triazete, [1,2,3]triazete, 1,4-dihydro-[1,2,3]triazete, [1,3]oxazetidine, 2H-[1,3]oxazete, [1,2]oxazetidine, 4H-[1,2]oxazete, 2H-[1,2]oxazete, [1,3]thiazetidine, 2H-[1,3]thiazete, [1,3]thiazete, [1,2]thiazetidine, 4H-[1,2]thiazete, 2H-[1,2]thiazete or [1,2]thiazete or azocane, azocane-2-one, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, [1,4]dioxocane, [1,4]oxazepane, [1,3]oxazepane, [1,4]oxazocane, [1,3]oxazocan-2-one, 5,6,7,8-tetrahydro-1H-azocin-2-one, thiacepane, , wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_4)-alkyl-O-(C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, -(C_1-C_4)-alkyl-OH or -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl, or

provided that R13 is -(C_0-C_3)-alkylene-O-R^{10} , or

provided that R11 is hydrogen atom and R12 is -O-(C_1-C_4)-alkyl,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4) The present invention also relates to the compounds of the formula I, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group azabenzimidazolyl, benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, 2-furyl, 3-furyl; imidazolyl, indolyl, indazolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrrolyl; 2-pyrrolyl, 3-pyrrolyl, quinolinyl, quinazolinyl, quinoxalinyl, tetrazolyl, thiazolyl, 2-thienyl or 3-thienyl,

which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,

phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is
1. fluor, chlor or brom,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. $-OCF_3$
8. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,
9. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
10. $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,
11. $-SO_2CH_3$ or
12. $-SO_2CF_3$,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, or -(C_1-C_6)-alkylene,

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15, -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond or –(C_1-C_4)-alkylene, or

R^1-N-R^2-V form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a het residue out of the group azaindole (1H-pyrrolopyridine), azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is as defined above and wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -(CH_2)$_m$-NR^{10}-SO_2-NR^{10}-(CH_2)$_n$-, -(CH_2)$_m$-CH(OH)-(CH_2)$_n$-, -(CH_2)$_m$-, -(CH_2)$_m$-O-(CH_2)$_n$-, -(CH_2)$_m$-C(O)-NR^{10} -(CH_2)$_n$-, -(CH_2)-SO_2-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-C(O)-NR^{10}-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-C(O)-(CH_2)$_n$-, -(CH_2)$_m$-C(O)-(CH_2)$_n$-,

-(CH_2)-S-(CH_2)$_n$-, -(CH_2)$_m$-SO_2-NR^{10}-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-SO_2-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-, -(CH_2)$_m$-O-C(O)-NR^{10}-(CH_2)$_n$- or –(CH_2)$_m$-NR^{10}-C(O)-O-(CH_2)$_n$-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) phenyl or naphthyl, wherein phenyl or naphthyl are unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiophene, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -O-R19, wherein R19 is

   a) hydrogen atom,

   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   d) -CF_3,

7) -CN,

8) -C(O)-O-C(R15, R16)-O-C(O)-R17,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-C(O)-R^{11}$,

12) $-C(O)-O-R^{11}$,

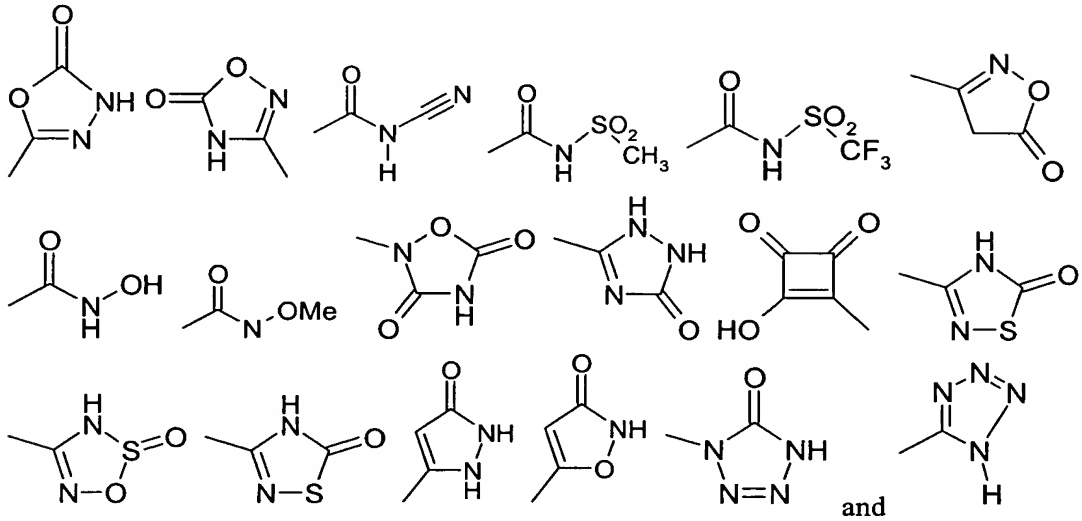
13) $-C(O)-N(R^{11})-R^{12}$,

14) $-N(R^{11})-R^{12}$,

15) $-NR^{10}-SO_2-R^{10}$,

16) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

17) a residue from the following list



and

wherein Me is methyl,

18) $-(C_1-C_4)$-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

19) $-(C_1-C_4)$-alkylene-C(O)-R^{11},

20) -(C_1-C_4)-alkylene-C(O)-O-R^{11},

21) -(C_1-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

22) -(C_1-C_4)-alkylene-N(R^{11})-R^{12},

23) -(C_0-C_2)-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

24) –(C_0-C_2)-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

25) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by R13,

26) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

27) -(C_0-C_4)-alkylene-(C_3-C_6)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

28) -(C_0-C_4)-alkylene-het, wherein het is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

29) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

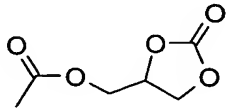
30) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

31) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-OH,

32) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R13,

33) -(C_0-C_4)-alkylene-N(R^{11})-R13,

34) the following residues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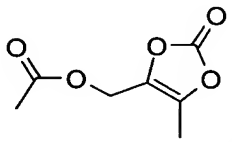

or

35) if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

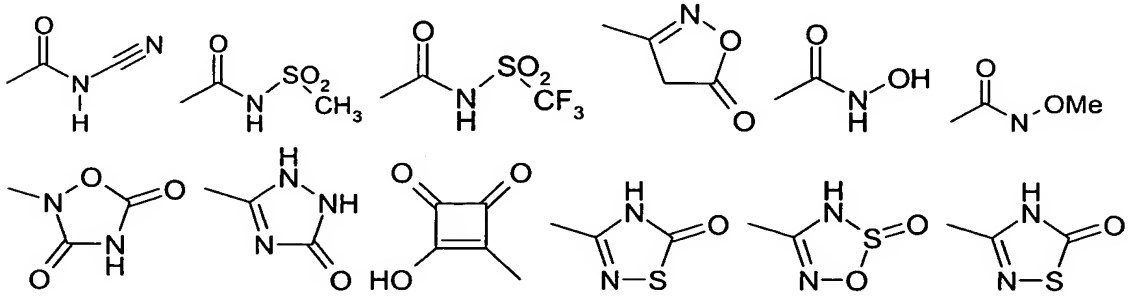
3) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein aryl is as defined above and wherein alkyl and aryl are independently from one another unsubstituted or mono-, di- or trisubstituted by R13,

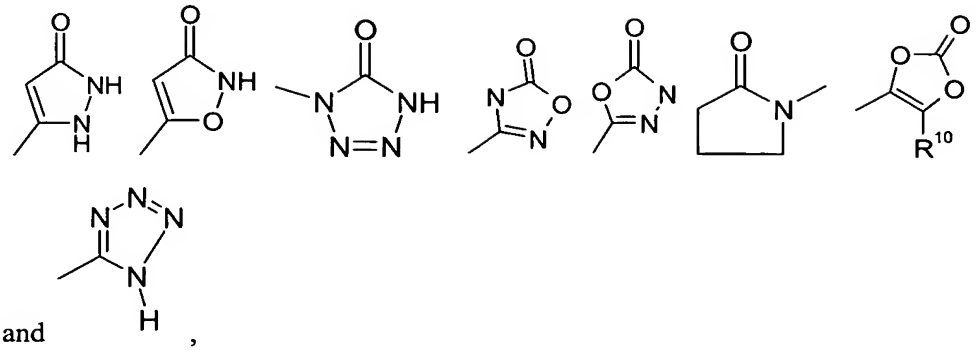
4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl is as defined above and independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, bromine, iodine, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_2$-R^{10}, -S-R^{10}, -SO_2-R^{10}, -S(O)$_2$-N(R^{10})-R^{20}, -C(O)-R^{10}, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-, -O-CF_3, -(C_1-C_3)-perfluoroalkyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, or a residue from the following list





and ,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together form a ring out of the droup cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 18) to 35), or

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered ring out of the group selected from azetidine, azete, [1,3]diazetidine, [1,3]diazete, [1,2,3]triazetidine, [1,2,3]triazete, [1,3]oxazetidine or [1,3]thiazetidine, or azocane, azocane-2-one, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, [1,4]oxazepane or [1,3]oxazepane, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_4)-alkyl-O-(C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, -(C_1-C_4)-alkyl-OH or -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl, or

provided that R13 is -(C_0-C_3)-alkylene-O-R^{10} , or

provided that R11 is hydrogen atom and R12 is -O-(C_1-C_4)-alkyl,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5) The present invention also relates to the compounds of the formula I, wherein

R0 is 1) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. F, Cl, Br or J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

Q is a direct bond, -C(O)-; $-SO_2-$ or $-(C_1-C_6)$-alkylene, $-(C_0-C_2)$-alkylene-C(O)-NR^{10}-,

R^1 is hydrogen atom, $-(C_1-C_2)$-alkyl, $-(C_1-C_3)$-alkylene-C(O)-NH-R0,

$-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-C(O)-O-R^{15}, $-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl or $-(C_1-C_3)$-alkylene-$S(O)_2-N(R^{4'})-R^{5'}$, wherein $R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or $-(C_1-C_4)$-alkyl,

R^2 is a direct bond or $-(C_1-C_2)$-alkylene,

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, 1,4-oxazepane, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, -OH, =O, -(C_1-C_8)-alkyl, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl,

-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -C(O)-NH_2 or –N(R^{18})-R^{21},

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_4)-alkyl,

V is 1. a cyclic residue out of the group containing compounds which are derived from azaindole (1H-pyrrolopyridine), aziridine, azirine, azetidine, azetidinone, 1,4-diazepane, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, 1,4-oxazepane, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,3-dioxolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiodiazole, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

G is a direct bond, -(CH_2)$_m$-, or -(CH_2)$_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,

2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone,

pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

4. (C_3-C_6)-cycloalkyl,

5. -C(O)-N(R^{11})-R^{12},

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -O-R19, wherein R19 is

   a) hydrogen atom,

   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

   d) -CF_3,

7) -CN,

8) -C(O)-O-C(R15, R16)-O-C(O)-R17,

9) -SO_s-R^{11}, wherein s is 1 or 2,

10) -SO_t-N(R^{11})-R^{12}, wherein t is 1 or 2,

11) -C(O)-R^{11},

12) -C(O)-O-R^{11},

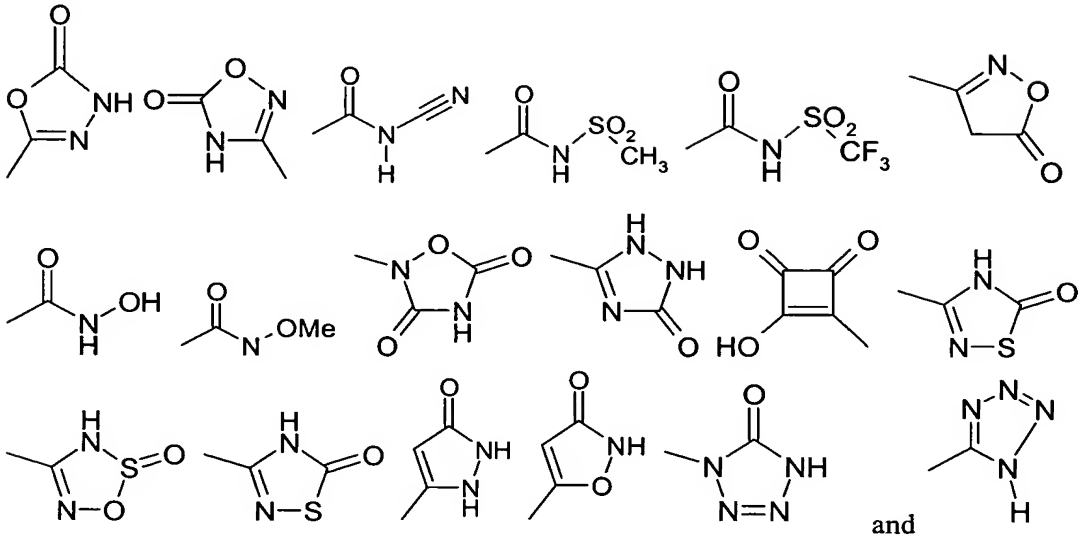
13) -C(O)-N(R^{11})-R^{12},

14) -N(R^{11})-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

17) a residue from the following list



and

wherein Me is methyl,

18) -(C_1-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

19) -(C_1-C_4)-alkylene-C(O)-R^{11},

20) -(C_1-C_4)-alkylene-C(O)-O-R^{11},

21) -(C_1-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

22) -(C_1-C_4)-alkylene-N(R^{11})-R^{12},

23) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

24) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

25) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

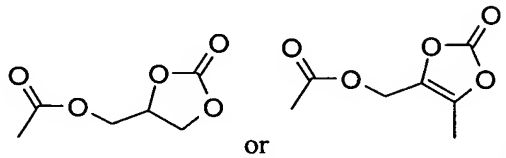
26) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

27) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-OH,

28) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R13,

29) -(C_0-C_4)-alkylene-N(R^{11})-R13,

30) the following residues



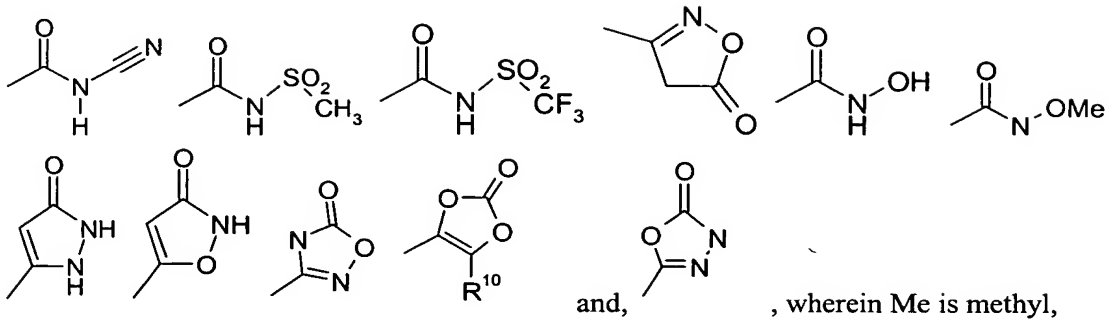
or or

31) if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_2$-R^{10}, -S-R^{10}, -SO_2-R^{10}, -S(O)$_2$-N(R^{10})-R^{20}, -C(O)-R^{10}, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-,

-O-CF_3, -(C_1-C_3)-perfluoroalkyl, -NH-C(O)-NH-R^{10}, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, -NH-C(O)-O-R^{10}, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together form a ring out of the droup cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 18) to 31), or

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered ring out of the group selected from azetidine, azete, [1,3]diazetidine, [1,3]diazete, [1,2,3]triazetidine, [1,2,3]triazete, [1,3]oxazetidine or [1,3]thiazetidine, or azocane, azocane-2-one, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, [1,4]oxazepane or [1,3]oxazepane, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_4)-alkyl-O-(C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, -(C_1-C_4)-alkyl-OH or

-(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl, or

provided that R13 is -(C_0-C_3)-alkylene-O-R^{10}, or

provided that R11 is hydrogen atom and R12 is -O-(C_1-C_4)-alkyl,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

6) The present invention also relates to the compounds of the formula I, wherein

R0 is 1) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyridyl, purinyl and pteridinyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

3) a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. is F, Cl, Br, J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

Q is a direct bond, -C(O)-; $-SO_2-$ or $-(C_1-C_6)$-alkylen, $-(C_0-C_2)$-alkylen-C(O)-NR^{10}-,

R^1 is hydrogen atom or $-(C_1-C_2)$-alkyl,

R^2 is a direct bond or $-(C_1-C_2)$-alkylen, or

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole,

isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluoro, chlorine, -(C_1-C_4)-alkyl or -NH_2,

V is 1. a cyclic residue out of the group containing compounds, which are derived from azaindolyl (1H-pyrrolopyridyl), azetidine, azepine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diazirine, 1,3-dioxolane, dioxazole, furan, imidazole, isoquinoline, isothiazole, isothiazolidine, isothiazoline, isoxazole, 2-isoxazoline, isoxazolidine, ketopiperazine, morpholine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, 1,2-oxathiolan, piperidine, pyran, pyrazine, pyrazole, pyridazine, piperazine, pyridine, pyridone, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, quinazoline, quinoline, tetrazine, tetrazole, thiadiazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thietan, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,

2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from 1,4-diazepane, ketomorpholine, thiophene, pyridazone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, thiadiazole or thiomorpholine, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

4. (C_3-C_6)-cycloalkyl,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

d) $-CF_3$,

7) -CN,

8) -C(O)-O-C(R15, R16)-O-C(O)-R17,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-C(O)-R^{11}$,

12) $-C(O)-O-R^{11}$,

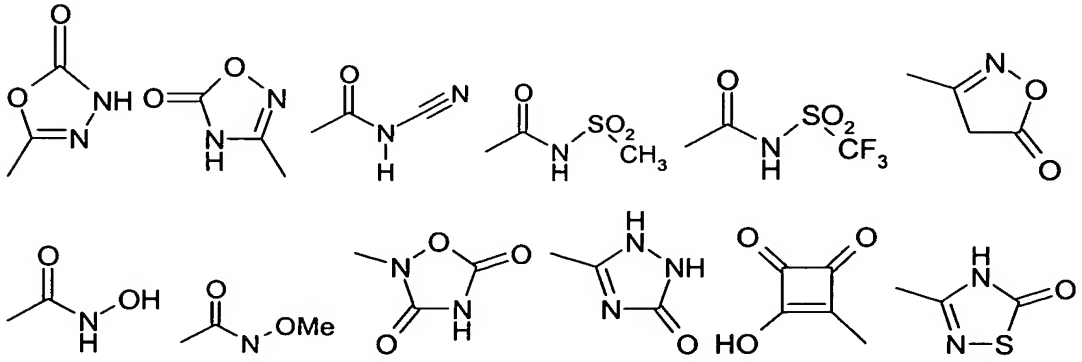
13) $-C(O)-N(R^{11})-R^{12}$,

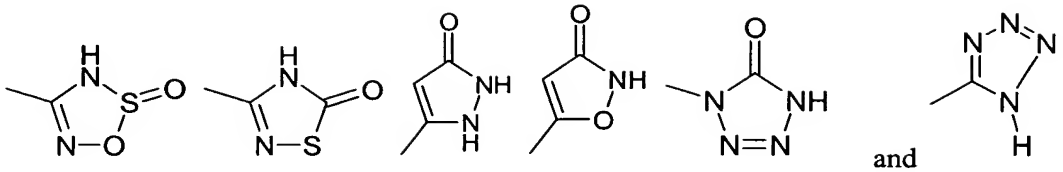
14) $-N(R^{11})-R^{12}$,

15) $-NR^{10}-SO_2-R^{10}$,

16) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

17) a residue from the following list





and

wherein Me is methyl,

18) -(C_1-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

19) -(C_1-C_4)-alkylene-C(O)-R^{11},

20) -(C_1-C_4)-alkylene-C(O)-O-R^{11},

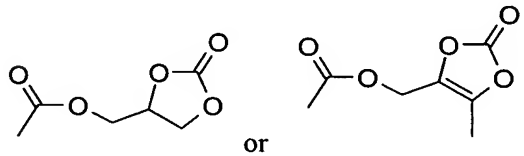
21) -(C_1-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

22) -(C_1-C_4)-alkylene-N(R^{11})-R^{12},

23) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

24) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl, or

25) the following residues



or

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,

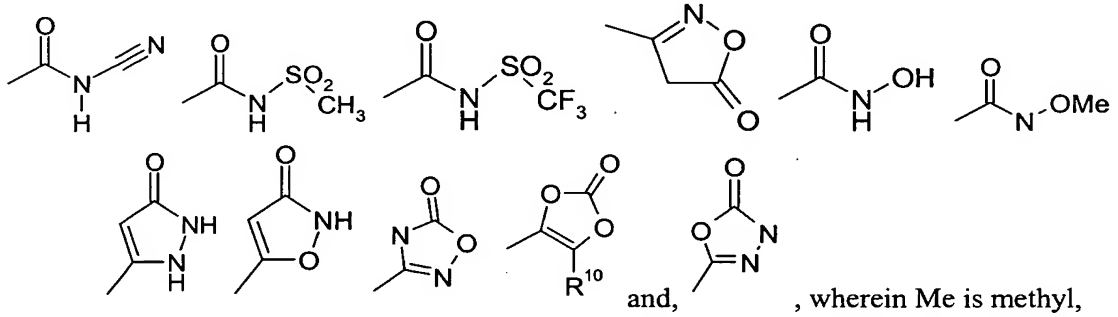
4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-

oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring, which is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine,

R13 is fluorine, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_3-C_6)$-cycloalkyl, $-(C_0-C_3)$-alkylene-O-R^{10}, $-Si-(CH_3)_3$, $-S-R^{10}$, $-SO_2-R^{10}$, $-(C_1-C_3)$-perfluoroalkyl, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl or $-(C_1-C_3)$-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl, or together form a ring out of the droup cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is $-(C_1-C_6)$-alkyl, $-(C_1-C_6)$-alkyl-OH, $-(C_1-C_6)$-alkyl-O-(C_1-C_6)-alkyl, $-(C_3-C_8)$-cycloalkyl, $-(C_1-C_6)$-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, $-(C_1-C_6)$-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, $-O-(C_1-C_4)$-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 18) to 25), or

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered ring out of the group selected from azetidine, azete, [1,3]diazetidine, [1,3]diazete, [1,2,3]triazetidine, [1,2,3]triazete, [1,3]oxazetidine or [1,3]thiazetidine, or azocane, azocane-2-one, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, [1,4]dioxocane, [1,4]oxazepane or [1,3]oxazepane, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_4)-alkyl-O-(C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, -(C_1-C_4)-alkyl-OH or -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

7) The present invention also relates to the compounds of the formula I, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl, wherein pyridyl is unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is F, Cl, Br, -OCH_3, -C(O)-NH_2 or –O-CF_3,

Q is a direct bond, -C(O)-; -SO_2-, -CH_2-C(O)-NH-, methylene or ethylene,

R^1 is hydrogen atom,

R^2 is a direct bond or methylene,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

R14 is fluorine, chlorine, methyl, ethyl or -NH_2,

V is 1. a residue out of the group containing compounds which is derived from azaindolyl (1H-pyrrolopyridyl), azetidine, 1,4-diazepane, isoxazole, isoquinoline, piperazine, piperidine, pyrazine, pyridazine, pyrimidine, pyrrolidine, quinazoline, quinoline or tetrahydropyrane,
wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,

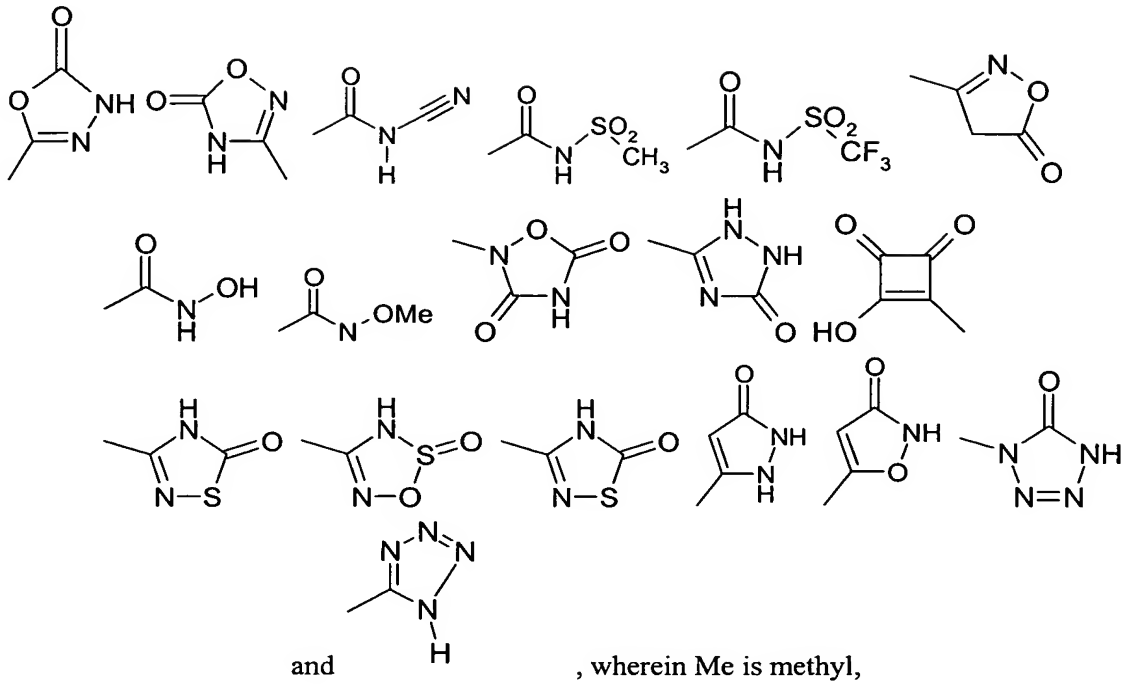
m is the integers zero, 1 or 2,

M is a hydrogen atom, (C_2-C_4)-alkyl, azepanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolyl, ketomorpholinyl, morpholinyl, [1,4]Oxazepanyl, piperidinyl, piperidonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolidinyl, 1,4,5,6-tetrahydro-

pyridazinyl, or tetrahydropyranyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are independently of one another selected from

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
6) -O-R19, wherein R19 is
   a) hydrogen atom,
   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or
   d) $-CF_3$,
7) -CN,
8) $-NR^{10}-SO_2-R^{10}$,
9) $-SO_s-R^{11}$, wherein s is 1 or 2,
10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,
11) $-C(O)-R^{11}$,
12) $-C(O)-O-R^{11}$,
13) $-C(O)-N(R^{11})-R^{12}$,
14) $-N(R^{11})-R^{12}$,
15) -C(O)-O-C(R15, R16)-O-C(O)-R17,
16) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,
17) a residue from the following list



and , wherein Me is methyl,

18) -(C_1-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

19) -(C_1-C_4)-alkylene-C(O)-R^{11},

20) -(C_1-C_4)-alkylene-C(O)-O-R^{11},

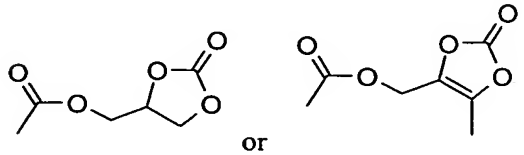
21) -(C_1-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

22) -(C_1-C_4)-alkylene-N(R^{11})-R^{12},

23) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

24) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl, or

25) the following residues



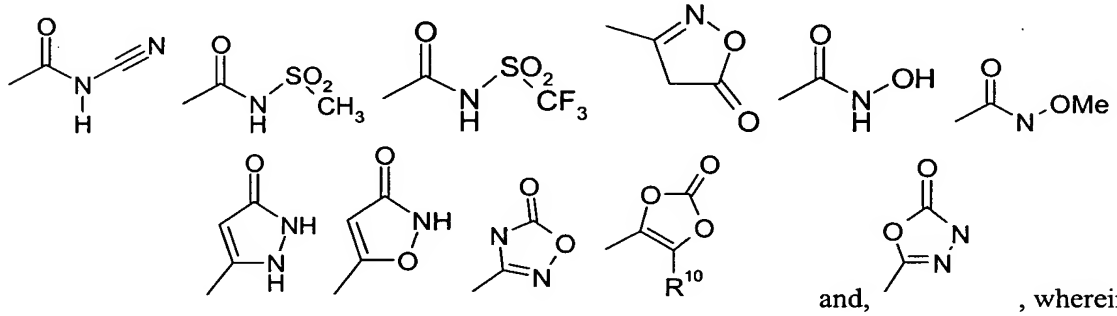
or

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,
2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,
4) -O-R^{17}, or
5) -(C_0-C_6)-alkyl-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane or pyrrolidine or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane piperazine, piperidine, pyrrolidine or thiomorpholine,

R13 is fluorine, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_3-C_6)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -(C_1-C_3)-perfluoroalkyl, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_4)-alkyl or -(C_1-C_3)-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, -(C_1-C_4)-alkyl, or together form a ring out of the droup cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

provided that at least one of the residues R^3, R^4, R^5, R^6 and R^7 is selected from the residues defined under 18) to 25), or

provided that R11 and R12 together with the nitrogen atom to which they are bonded form a 4- or 8-membered ring out of the group selected from azetidine or [1,4]oxazepane, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

provided that R17 is -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

Detailed Description of the Invention

The present invention also relates to the compounds of the formula I, which are

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)- 1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxymethyl-pyrrolidine-1- carbonyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid 2-oxo-[1,3]dioxolan-4-ylmethyl ester;

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-indole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-5-carboxylic acid 1-(2-methoxy-ethoxycarbonyloxy)-ethyl ester;

1-[(6-Chloro-pyridin-3-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-indole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-indole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

4-(3-Methoxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 5- (isopropoxy-amide) 2-[(1-isopropyl-piperidin-4-yl)-amide];

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H- indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)- 1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide;

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-4-carboxylic acid 1-(2-methoxy-ethoxycarbonyloxy)-ethyl ester;

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-4-carboxylic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester; or

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester.

Definition of Terms

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

The term "alkyl" is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue or an arylalkyl residue. Examples of "-(C_1-C_8)-alkyl" or "-(C_1-C_8)-alkylene" are alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms are methyl, methylene, ethyl, ethylene, propyl, propylene, butyl, butylene, pentyl, pentylene, hexyl, heptyl or octyl, the n-

isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tBu, tert-pentyl, sec-butyl, tert-butyl or tert-pentyl. The term "-(C_0-C_6)-alkyl" or „-(C_0-C_8)-alkylene" is a hydrocarbon residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. The term "-C_0-alkyl" or "-C_0-alkylene" is a covalent bond.

"Unsaturated alkyl residues" are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl. Alkyl residues can also be unsaturated when they are substituted.

Examples of -(C_3-C_8)-cycloalkyl cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyloheptyl or cyclooctyl, which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

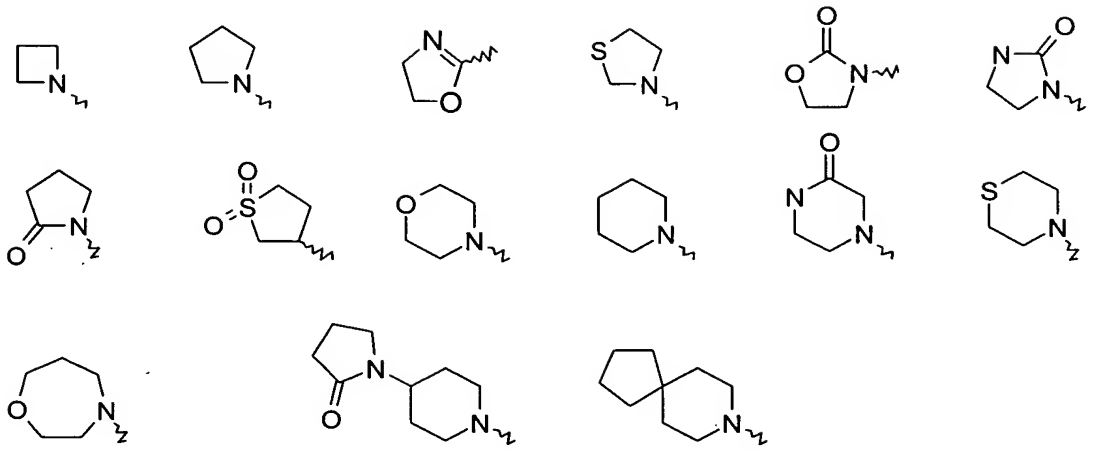
Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C_1-C_8)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_8)-alkyl, (C_3-C_6)-cycloalkyl, and unsaturated (C_2-C_8)-alkyl like (C_2-C_8)-alkenyl or (C_2-C_8)-alkynyl. Similarly, a group like (C_1-C_4)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_4)-alkyl, and unsaturated (C_2-C_4)-alkyl like (C_2-C_4)-alkenyl or (C_2-C_4)-alkynyl.

The terms "a monocyclic or bicyclic 6- to 14-membered aryl" or "-(C_6-C_{14})-aryl" are understood as meaning aromatic hydrocarbon radicals containing from 6 to 14 carbon atoms in the ring. Examples of -(C_6-C_{14})-aryl radicals are phenyl, naphthyl, for example 1-naphthyl and 2-naphthyl, biphenylyl, for example 2-biphenylyl, 3-biphenylyl and 4-biphenylyl, anthryl or fluorenyl. Biphenylyl radicals, naphthyl radicals and, in particular, phenyl radicals are preferred aryl radicals.

The terms "mono- or bicyclic 4- to 15-membered heterocyclyl" or "-(C_4-C_{15})-heterocyclyl" refer to heterocycles in which one or more of the 4 to 15 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur.

Examples are acridinyl, azaindole (1H-pyrrolopyridinyl), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxazolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, oxetanyl, oxocanyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred are heterocyclyls, such as benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, 2-furyl, 3-furyl; imidazolyl, indolyl, indazolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrrolyl; 2-pyrrolyl, 3-pyrrolyl, quinolinyl, quinazolinyl, quinoxalinyl, tetrazolyl, thiazolyl, 2-thienyl and 3-thienyl.

Also preferred are:



The terms "het" or "a 3- to 7-membered cyclic residue containing up to 1, 2, 3 or 4 heteroatoms" refer to structures of heterocycles which can be derived from compounds such as azepine, azetidine, aziridine, azirine, 1,4 diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxetan, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole.

The term " R^1-N-R^2-V can form a 4- to 8-membered cyclic group " or "R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen" refer to structures of heterocycles which can be derived from compounds such as azepane, azepine, azete, azetidine, azocane, [1,3]diazete, [1,3]diazetidine, [1,4]diazocane, [1,5]diazocane , 1,2-dihydro-[1,3]diazete, 1,2-dihydro-azete, 2,3-dihydro-azete, 1,2-dihydro-[1,2,3]triazete, 1,4-dihydro-[1,2,3]triazete, dioxazole, dioxazine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine,

[1,3]oxazepane, [1,4]oxazepane, 2H-[1,2]oxazete, 4H-[1,2]oxazete, 2H-[1,3]oxazete, [1,2]oxazetidine, [1,3]oxazetidine, [1,4]oxazocane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiacepane, [1,2]thiazete, [1,3]thiazete, 4H-[1,2]thiazete, 2H-[1,2]thiazete 2H-[1,3]thiazete, [1,2]thiazetidine, [1,3]thiazetidine, [1,4]thiazocane, [1,5]thiazocane, thiazolidine, thiazoline, thiomorpholine, [1,2,3]triazete, [1,2,3]triazetidine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole.

The term "R^{15} and R^{16} together with the carbon atom to which they are bonded can form a 3- to 6 membered carbocyclic ring" refer to structures, which can be derived from compounds such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "R^1 and R^7 together with the atoms to which they are bonded can form a 6- to 8-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen" refers to structures of heterocycles which can be derived from compounds such as azocane, azocane-2-one, cyloheptyl cyclohexyl, cyclooctane, cyclooctene, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazine, [1,4]dioxocane, dioxole, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, [1,4]oxazocane, [1,3]oxazocan-2-one, oxocane, oxocan-2-one, phenyl, piperazine, piperidine, pyran, pyrazine, pyridazine, pyrimidine, 5,6,7,8-tetrahydro-1H-azocin-2-one or thiomorpholine.

The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the, the 4-15 membered mono- or polycyclic group could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 4-15 membered mono- or polycyclic group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine,

perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

The term "-(C_1-C_3)-perfluoroalkyl" is a partial or totally fluorinated alkyl-residue, which can be derived from residues such as $-CF_3$, $-CHF_2$, $-CH_2F$, $-CHF-CF_3$, $-CHF-CHF_2$, $-CHF-CH_2F$, $-CH_2-CF_3$, $-CH_2-CHF_2$, $-CH_2-CH_2F$, $-CF_2-CF_3$, $-CF_2-CHF_2$, $-CF_2-CH_2F$, $-CH_2-CHF-CF_3$, $-CH_2-CHF-CHF_2$, $-CH_2-CHF-CH_2F$, $-CH_2-CH_2-CF_3$, $-CH_2-CH_2-CHF_2$, $-CH_2-CH_2-CH_2F$, $-CH_2-CF_2-CF_3$, $-CH_2-CF_2-CHF_2$, $-CH_2-CF_2-CH_2F$, $-CHF-CHF-CF_3$, $-CHF-CHF-CHF_2$, $-CHF-CHF-CH_2F$, $-CHF-CH_2-CF_3$, $-CHF-CH_2-CHF_2$, $-CHF-CH_2-CH_2F$, $-CHF-CF_2-CF_3$, $-CHF-CF_2-CHF_2$, $-CHF-CF_2-CH_2F$, $-CF_2-CHF-CF_3$, $-CF_2-CHF-CHF_2$, $-CF_2-CHF-CH_2F$, $-CF_2-CH_2-CF_3$, $-CF_2-CH_2-CHF_2$, $-CF_2-CH_2-CH_2F$, $-CF_2-CF_2-CF_3$, $-CF_2-CF_2-CHF_2$ or $-CF_2-CF_2-CH_2F$.

The term "-(C_1-C_3)-perfluoroalkylene" is a partial or totally fluorinated alkylene-residue, which can be derived from residues such as $-CF_2-$, -CHF-, $-CHF-CHF_2-$, -CHF-CHF-, $-CH_2-CF_2-$, $-CH_2-CHF-$, $-CF_2-CF_2-$, $-CF_2-CHF-$, $-CH_2-CHF-CF_2-$, $-CH_2-CHF-CHF-$, $-CH_2-CH_2-CF_2-$, $-CH_2-CH_2-CHF$, $-CH_2-CF_2-CF_2-$, $-CH_2-CF_2-CHF-$, $-CHF-CHF-CF_2-$, -CHF-CHF-CHF-, $-CHF-CH_2-CF_2-$, $-CHF-CH_2-CHF-$, $-CHF-CF_2-CF_2-$, $-CHF-CF_2-CHF-$, $-CF_2-CHF-CF_2-$, $-CF_2-CHF-CHF-$, $-CF_2-CH_2-CF_2-$, $-CF_2-CH_2-CHF-$, $-CF_2-CF_2-CF_2-$, or $-CF_2-CF_2-CHF$.

The term "oxo-residue" or "=O" refers to residues such as carbonyl (-C(O)-) or nitroso (-N=O). Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, particularly preferably chlorine or bromine.

Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

"Physiologically tolerable salts" of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxyl group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds of the formula I, which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxyl group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

"Salts" of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiologically tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts.
The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols.

The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives, as well as active metabolites of the compounds of the formula I. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I, which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups and the guanidino group and also ester prodrugs and amide prodrugs of carboxylic acid groups which may be present in compounds of the formula I. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or a carbamate, preferably a -(C_1-C_6)-alkyloxycarbonyl group. Suitable acyl groups and carbamate groups for acyl prodrugs and carbamate prodrugs are, for example, the groups R^{p1}-CO- and R^{p2}O-CO-, in which R^{p1} is hydrogen, (C_1-C_{18})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl-, (C_6-C_{14})-aryl, Het-, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl- or Het-(C_1-C_4)-alkyl- and in which R^{p2} has the meanings indicated for R^{p1} with the exception of hydrogen.

Especially preferred compounds of the formula I are those wherein two or more residues are defined as indicated before for preferred compounds of the formula I, or residues can have one or some of the specific denotations of the residues given in their general definitions or in the definitions of preferred compounds before. All possible combinations of definitions given for preferred definitions and of specific denotations of residues explicitly are a subject of the present invention.

Also with respect to all preferred compounds of the formula I all their stereoisomeric forms and mixtures thereof in any ratio and their physiologically acceptable salts explicitly are a subject of the present invention, as well as are their prodrugs. Similarly, also in all preferred compounds of the formula I, all residues that are present more than one time in the molecule are independent of each other and can be identical or different.

The compounds of the formula I can be prepared by utilizing procedures and techniques, which per se are well known and appreciated by one of ordinary skill in the art. Starting materials or building

blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature. Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in the literature, or by procedures or analogously to procedures described in this application.

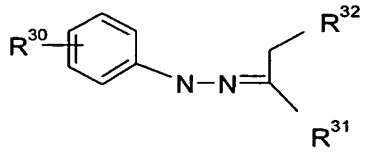
In general, compounds of the formula I can be prepared, for example in the course of a convergent synthesis, by linking two or more fragments which can be derived retrosynthetically from the formula I. More specifically, suitably substituted starting indole derivatives are employed as building blocks in the preparation of the compounds of formula I. If not commercially available, such indole derivatives can be prepared according to the well-known standard procedures for the formation of the indole ring system such as, for example, the Fischer indole synthesis, the Madelung indole synthesis, the indole synthesis starting from N-chloroanilines and β-ketosulfides described by Gassman et al., the Bischler indole synthesis, the Reissert indole synthesis, or the Nenitzescu indole synthesis. By choosing suitable precursor molecules, these indole syntheses allow the introduction of a variety of substituents into the various positions of the indole system which can then be chemically modified in order to finally arrive at the molecule of the formula I having the desired substituent pattern. As one of the comprehensive reviews in which numerous details and literature references on the chemistry of indoles and on synthetic procedures for their preparation can be found, W. J. Houlihan (ed.),"Indoles, Part One", volume 25, 1972, out of the series "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor (ed.), John Wiley & Sons, is referred to.

Examples of the many commercially available indole derivatives that are suitable as starting materials for the preparation of the compounds of formula I, are the following (the acids listed are commercially available as the free acids themselves and/or as the methyl or ethyl esters): indole-2-carboxylic acid, indole-3-carboxylic acid, indole-3-acetic acid, 3-(3-indolyl)-propionic acid, indole-2,3-dicarboxylic acid, 3-ethoxycarbonylmethyl-indole-2-carboxylic acid, 3-methyl-indole-2-carboxylic acid, 5-fluoroindole-2-carboxylic acid, 5-chloro-indole-2-carboxylic acid, 5-bromo-indole-2-carboxylic acid, 5-methoxy-indole-2-carboxylic acid, 5-hydroxy-indole-2-carboxylic acid, 5,6-dimethoxy-indole-2-carboxylic acid, 4-benzyloxy-indole-2-carboxylic acid, 5-benzyloxy-indole-2-carboxylic acid, 6-benzyloxy-5-methoxy-indole-2-carboxylic acid, 5-methyl-indole-2-carboxylic acid, 5-ethyl-indole-2-carboxylic acid, 7-methyl-indole-2-carboxylic acid, 4-methoxy-indole-2-carboxylic acid, 6-methoxy-indole-2-carboxylic acid, 4,6-dimethoxy-indole-2-carboxylic acid, 4,6-dichloro-indole-2-carboxylic acid, 5-nitro-indole-2-carboxylic acid, 5-methylsulfonyl-indole-2-carboxylic acid, 7-nitro-indole-2-carboxylic acid, 7-tert-butylcarbonylamino-indole-2-carboxylic acid, 7-(3-trifluoro-

methylbenzoylamino)-indole-2-carboxylic acid, 7-(4-methoxyphenylsulfonylamino)-indole-2-carboxylic acid, 5-bromo-3-methyl-indole-2-carboxylic acid, 3-(2-carboxyethyl)-6-chloroindole-2-carboxylic acid.

If starting indole derivatives are to be synthesized this can be done, for example, according to the well known indole syntheses mentioned above. In the following they are explained briefly, however, they are standard procedures comprehensively discussed in the literature, and are well known to one skilled in the art.

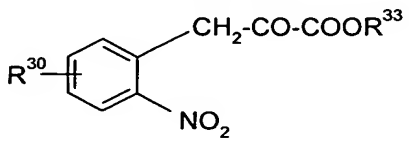
The Fischer indole synthesis comprises the acid cyclization of phenylhydrazones, for example of the general formula **2**,



2

which can be obtained by various methods and in which R^{30}, R^{31} and R^{32} and n can have a wide variety of denotations. Besides hydrogen and alkyl, R^{31} and R^{32} can especially denote ester groups or methyl or ethyl groups or 2,2,2- trifluoroethyl groups carrying an ester group as substituent thus allowing the introduction into the indole molecule of the $(CH_2)_p$-CO moiety occurring in the groups R^2 and/or R^3 in the compounds of the formula I. As examples of the many literature references describing the synthesis of indole derivatives according to the Fischer synthesis, besides the above-mentioned book edited by Houlihan, the following articles are mentioned: F.G. Salituro et al., J. Med. Chem. 33 (1990) 2944; N.M. Gray et al., J. Med. Chem. 34 (1991) 1283; J. Sh. Chikvaidze et al., Khim. Geterotsikl. Soedin. (1991) 1508; S. P. Hiremath et al., Indian J. Chem. 19 (1980) 770; J. Bornstein, J. Amer. Chem. Soc. 79 (1957) 1745; S. Wagaw, B. Yang and S. Buchwald, J. Am. Chem. Soc. 121 (1999) 10251 or by Y. Murakami, Y. Yokoyama, T. Miura, H. Hirasawa Y. Kamimura and M. Izaki, Heterocycles 22 (1984) 1211.

The Reissert indole synthesis comprises the reductive cyclization of o-nitrophenylpyruvic acids or esters thereof, for example of the general formula **3**,

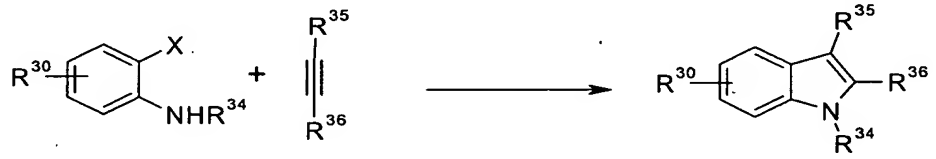


3

in which the groups R^{30} can have a wide variety of denotations and can be present in all positions of the benzene ring. The Reissert indole synthesis leads to derivatives of indole-2-carboxylic acids. The

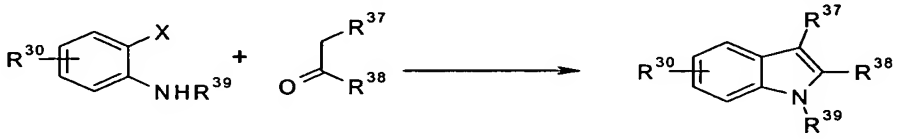
pyruvic acid derivatives of the formula **3** can be obtained by condensation of oxalic acid esters with substituted o-nitrotoluenes. As literature references, besides the above-mentioned book edited by Houlihan and the literature articles mentioned therein, for example the articles by H. G. Lindwall and G. J. Mantell, J. Org. Chem. 18 (1953) 345 or by H. Burton and J. L. Stoves, J. Chem. Soc. (1937) 1726 or by W. Noland, F. Baude, Org. Synth Coll. Vol. V, J. Wiley, New York, (1973) 567 are mentioned.

Another method to gain regioselective access to the indole structure involves palladium catalysis, for example o-haloanilines (X = Cl, Br, I) or o-trifluoromethanesufonyloxyanilines (X = OTf) of the general formula **4** can be cyclized to indoles utilizing several alkynes by adopting procedures described by J. Ezquerra, C. Pedregal. C. Lamas, J. Barluenga, M. Pérez, M. Garcia-Martin, J. Gonzalez, J. Org. Chem. 61 (1996) 5805; or F. Ujjainwalla, D. Warner, Tetrahedron Lett. 39 (1998) 5355 and furthermore A. Rodriguez, C. Koradin, W. Dohle, P. Knochel, Angew. Chem. 112 (2000) 2607; or R. Larock, E. Yum, M. Refvik, J. Org. Chem. 63 (1998) 7653; R. Larock, E. Yum, J. Am. Chem. Soc. 113 (1991) 6689; K. Roesch; R. Larock, J. Org. Chem. 66 (2001) 412.



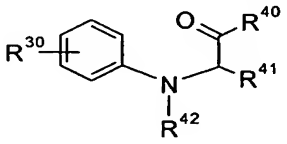
4 **5** **6**

Alternatively the indole structure can be built up by employment of a variety of ketones under palladium catalysis by adopting and modifying a procedure described by C. Chen, D. Liebermann, R. Larsen, T. Verhoeven and P. Reider J. Org. Chem. 62 (1997) 2676 as indicated below:



7 **8** **9**

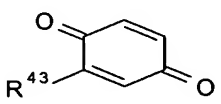
According to the Bischler indole synthesis α-anilinoketones, for example of the general formula **10**,



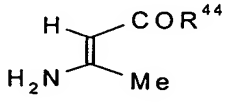
10

can be cyclized to indole derivatives.

The Nenitzescu indole synthesis provides a valuable route to indole-3-carboxylic acid derivatives carrying a hydroxy group in the 5-position. It comprises the reaction of a para-benzoquinone with a ∃-aminocrotonate, for example of the compounds of the formulae **11** and **12**.

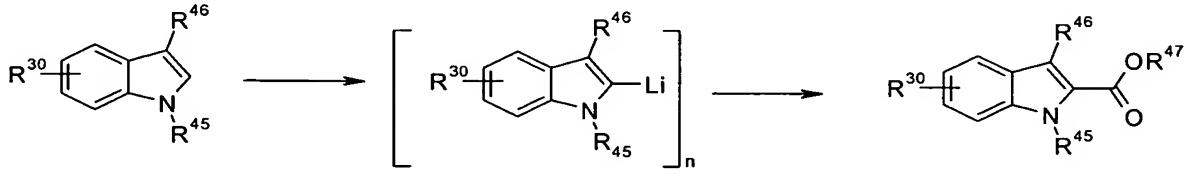


11



12

A further route to specifically substituted indole derivatives proceeds via 2,3-dihydroindoles (indolines) which can be easily obtained by reduction of indoles, for example by hydrogenation, or by cyclization of suitable phenylethylamine derivatives. Indolines can undergo a variety of electrophilic aromatic substitution reaction allowing the introduction of various substituents into the benzene nucleus which cannot directly be introduced by such reactions into the benzene nucleus of the indole molecule. The indolines can then be dehydrogenated to the corresponding indoles, for example with reagents like chloranil, or palladium together with a hydrogen acceptor. Again, details on these syntheses can be found in the above-mentioned book edited by Houlihan.



13 **16** **17**

Moreover 2-H-indoles can be converted into the corresponding carboxylic acids or carboxylic esters by lithiation of the 2-position of the indoles of the general formula **13** and subsequent reaction with carbon dioxide or alkylchloroformate according to I. Hasan, E. Marinelli, L. Lin, F. Fowler, A. Levy, J. Org. Chem. 46 (1981) 157; T. Kline J. Heterocycl. Chem. 22 (1985) 505; J.-R. Dormoy, A. Heymes, Tetrahedron 49, (1993) 2885; E. Desarbre, S. Coudret, C. Meheust, J.-Y. Mérour, Tetrahedron 53 (1997) 3637 as indicated below:

R^{45} denotes for Hydrogen or a protecting group like for example benzenesulfonyl or tert-butoxycarbonyl.

Depending on the substituents in the starting materials, in certain indole syntheses mixtures of positional isomers may be obtained which, however, can be separated by modern separation techniques like, for example, preparative HPLC.

Further, in order to obtain the desired substituents in the benzene nucleus and in the heterocyclic nucleus of the indole ring system in the formula I, the functional groups introduced into the ring system during the indole synthesis can be chemically modified. For example, indoles carrying a hydrogen atom in the 2-position or the 3-position can also be obtained by saponification and subsequent decarboxylation of indoles carrying an ester group in the respective position. Carboxylic acid groups and acetic acid groups in the 2-position and the 3-position can be converted into their homologues by usual reactions for chain elongation of carboxylic acids. Halogen atoms can be introduced into the 2-position or the 3-position, for example by reacting the respective indolinone with a halogenating agent such as phosphorus pentachloride analogously to the method described by J. C. Powers, J. Org. Chem. 31 (1966) 2627. The starting indolinones for such a synthesis can be obtained from 2-aminophenyl acetic acids. Starting indole derivatives for the preparation of compounds of the formula I carrying a halogen substituent in the 3-position can also be obtained according to procedures described in the literature like the following. For the fluorination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position N-fluoro-2,4,6-trimethylpyridinium triflate is the reagent of choice (T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita J. Am. Chem. Soc. 112 (1990) 8563). Chlorination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position by reaction with sulfuryl chloride in benzene yields 3-chloro-1H-indole-2-carboxylic acid ethyl ester (Chem. Abstr. 1962, 3441i - 3442b); the same result can obtained by means of NCS (D. Comins, M. Killpack, Tetrahedron Lett. 33 (1989) 4337; M. Brennan, K. Erickson, F. Szmlac, M. Tansey, J. Thornton, Heterocycles 24 (1986) 2879). Bromination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position can be achieved by reaction with NBS (M. Tani, H. Ikegami, M. Tashiro, T. Hiura, H. Tsukioka, Heterocycles 34 (1992) 2349). Analogously to the procedures described above NIS can be used efficiently for the iodination in the of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position. Furthermore the iodination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position the use of iodine is efficient (T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka Chem. Pharm. Bull. 36 (1988) 2248).

Especially the groups present in the indole ring system can be modified by a variety of reactions and thus the desired residues R^{1a}, R^{1b}, R^{1c}, R^{1d} and R^{1e} be obtained. For example, nitro groups can be reduced to amino group with various reducing agents, such as sulfides, dithionites, complex hydrides or by catalytic hydrogenation. A reduction of a nitro group may also be carried out at a later stage of the synthesis of a compound of the formula I, and a reduction of a nitro group to an amino group may also occur simultaneously with a reaction performed on another functional group, for example when reacting a group like a cyano group with hydrogen sulfide or when hydrogenating a group. In order to introduce or derive the residues R^{1a-e}, amino groups can then be modified according to standard

procedures for alkylation, for example by reaction with (substituted) alkyl halogenides or by reductive amination of carbonyl compounds, according to standard procedures for acylation, for example by reaction with activated carboxylic acid derivatives such as acid chlorides, anhydrides, activated esters or others or by reaction with carboxylic acids in the presence of an activating agent, or according to standard procedures for sulfonylation, for example by reaction with sulfonyl chlorides. Carboxylic acids, carboxylic acid chlorides or carboxylic acid esters can be introduced by procedures described by F. Santangelo, C. Casagrande, G. Norcini, F. Gerli, Synth. Commun. 23 (1993) 2717; P. Beswick, C. Greenwood, T. Mowlem, G. Nechvatal, D. Widdowson, Tetrahedron 44 (1988) 7325; V. Collot, M. Schmitt, P. Marwah, J. Bourguignon, Heterocylces 51 (1999) 2823. Halogens or hydroxy groups – via the triflate or nonaflate – or primary amines - via its diazonium salt – or after interconversion to the corresponding stannane, or boronic acid - present in the indole structure can be converted into a variety of other functional groups like for example –CN, $-CF_3$, Ethers, acids, esters, amides, amines, alkyl- or aryl groups mediated by means of transition metals, namely palladium or nickel catalysts or copper salts and reagents for example referred to below (F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 110 (1998) 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 576 (1999) 125; T. Sakamoto, K. Ohsawa, J. Chem. Soc. Perkin Trans I, (1999), 2323; D. Nichols, S. Frescas, D. Marona-Lewicka, X. Huang, B. Roth, G. Gudelsky, J. Nash, J. Med. Chem, 37 (1994), 4347; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett., 39 (1998) 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 39 (1998) 2933; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; A. Klaspars, X. Huang, S. Buchwald, J. Am. Chem. Soc. 124 (2002) 7421; F. Kwong, A. Klapars, S. Buchwald, Org. Lett. 4 (2002) 581; M Wolter, G. Nordmann, G. Job, S. Buchwald, 4 (2002) 973)

Ester groups present in the benzene nucleus can be hydrolyzed to the corresponding carboxylic acids, which after activation can then be reacted with amines or alcohols under standard conditions. Ether groups present at the benzene nucleus, for example benzyloxy groups or other easily cleavable ether groups, can be cleaved to give hydroxy groups which then can be reacted with a variety of agents, for example etherification agents or activating agents allowing replacement of the hydroxy group by other groups. Sulfur-containing groups can be reacted analogously.

During the course of the synthesis in order to modify the groups R^{50} or $R^{8'}$ attached to the indole ring system by application of parallel synthesis methodology, beside a variety of reactions, palladium or copper salt catalysis can be extremely useful. Such reactions are described for example in F.

Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 110 (1998), 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 576 (1999) 125; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett. 39 (1998) 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 39 (1998) 2933; J. Wolfe, H. Tomori, J. Sadight, J. Yin, S. Buchwald, J. Org. Chem. 65 (2000) 1158; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; A. Klaspars, X. Huang, S. Buchwald, J. Am. Chem. Soc. 124 (2002) 7421; F. Kwong, A. Klapars, S. Buchwald, Org. Lett. 4 (2002) 581; M Wolter, G. Nordmann, G. Job, S. Buchwald, 4 (2002) 973).

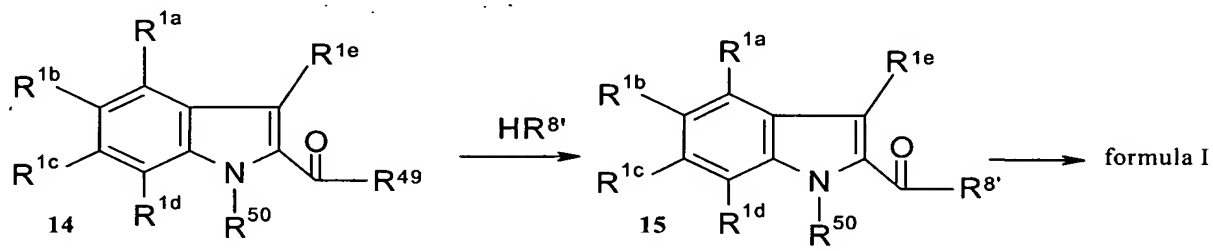
The previously-mentioned reactions for the conversion of functional groups are furthermore, in general, extensively described in textbooks of organic chemistry like M. Smith, J. March, March's Advanced Organic Chemistry, Wiley-VCH, 2001 and in treatises like Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany, or "Organic Reactions", John Wiley & Sons, New York, or R. C. Larock, " Comprehensive Organic Transformations", Wiley-VCH, 2nd ed (1999), B. Trost, I. Fleming (eds.) Comprehensive Organic Synthesis, Pergamon,1991; A. Katritzky, C. Rees, E. Scriven Comprehensive Heterocyclic Chemistry II, Elsevier Science, 1996) in which details on the reactions and primary source literature can be found. Due to the fact that in the present case the functional groups are attached to an indole ring it may in certain cases become necessary to specifically adapt reaction conditions or to choose specific reagents from a variety of reagents that can in principle be employed in a conversion reaction, or otherwise to take specific measures for achieving a desired conversion, for example to use protecting group techniques. However, finding out suitable reaction variants and reaction conditions in such cases does not cause any problems for one skilled in the art.

The structural elements present in the residues in the 1-position of the indole ring in the compounds of the formula I and in the COR^8 group present in the 2-position and/or in the 3-position of the indole ring can be introduced into the starting indole derivative obtainable as outlined above by consecutive reaction steps using parallel synthesis methodologies like those outlined below using procedures which per se are well known to one skilled in the art.

The residues $R^{8'}$ that can be introduced in formula **14**, for example, by condensing a corresponding carboxylic acid of the formula **14** with a compound of the formula $HR^{8'}$,

i. e. with an amine of the formula $HN(R^{1'})R^{2'}$–V-G-M to give a compound of the formula **15**. The compound of the formula **15** thus obtained can already contain the desired final groups, i. e. the

groups $R^{8'}$ and R^{50} can be the groups $-N(R^{1})R^{2}$–V-G-M and R^{0}-Q- as defined in the formula I, or optionally in the compound of the formula **15** thus obtained subsequently the residue or the residues $R^{8'}$ and the residue R^{50} are converted into the residues $-N(R^{1})R^{2}$–V-G-M and R^{0}-Q- , respectively, to give the desired compound of the formula I.



Thus, the residues $R^{8'}$ and the residues $R^{1'}$ and $R^{2'}$–V-G-M contained therein can have the denotations of R^{1} and R^{2}–V-G-M, respectively, given above or in addition in the residues $R^{1'}$ and $R^{2'}$–V-G-M functional groups can also be present in the form of groups that can subsequently be transformed into the final groups R^{1} and R^{2}–V-G-M, i. .e. functional groups can be present in the form of precursor groups or of derivatives, for example in protected form. In the course of the preparation of the compounds of the formula I it can generally be advantageous or necessary to introduce functional groups which reduce or prevent undesired reactions or side reactions in the respective synthesis step, in the form of precursor groups which are later converted into the desired functional groups, or to temporarily block functional groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley, 1991, or P. Kocienski, Protecting Groups, Thieme 1994). As examples of precursor groups cyano groups and nitro groups may be mentioned. The cyano group can in a later step be transformed into carboxylic acid derivatives or by reduction into aminomethyl groups, or the nitro groups may be transformed by reduction like catalytic hydrogenation into amino groups. Protective groups can also have the meaning of a solid phase, and cleavage from the solid phase stands for the removal of the protective group. The use of such techniques is known to those skilled in the art (Burgess K (Ed.) Solid Phase Organic Synthesis ,New York: Wiley, 2000). For example, a phenolic hydroxy group can be attached to a trityl-polystyrene resin, which serves as a protecting group, and the molecule is cleaved from this resin by treatment with TFA at a later stage of the synthesis.

The residue R^{50} in the compounds of the formulae **14** and **15** can denote the group -Q-R^{0} as defined above which finally is to be present in the desired target molecule of the formula I, or it can denote a group which can subsequently be transformed into the group -Q-R^{0}, for example a precursor group or

a derivative of the group -Q-R^0 in which functional groups are present in protected form, or R^{50} can denote a hydrogen atom or a protective group for the nitrogen atom of the indole ring. Similarly, the residues R^{1e}, R^{1a}, R^{1b}, R^{1c} and R^{1d} in the formulae **14** and **15** have the corresponding definitions of R^7, R^6, R^5, R^4, and R^3 in formula I as defined above, however, for the synthesis of the compounds of the formula I these residues, too, can in principle be present at the stage of the condensation of a compound of the formula **14** with a compound of the formula $HR^{8'}$ giving a compound of the formula **15** in the form of precursor groups or in protected form.

The residues R^{49} in the compounds of the formula **14** which can be identical or different, can be, for example, hydroxy or (C_1-C_4)-alkoxy, i. e., the groups COR^{49} present in the compounds of the formula **14** can be, for example, the free carboxylic acids or esters thereof like alkyl esters as can be the groups COR^8 in the compounds of the formula I. The groups COR^{49} can also be any other activated derivative of a carboxylic acid which allows amide formation, ester formation or thioester formation with a compound of the formula $HR^{8'}$. The group COR^{49} can be, for example, an acid chloride, an activated ester like a substituted phenyl ester, an azolide like an imidazolide, an azide or a mixed anhydride, for example a mixed anhydride with a carbonic acid ester or with a sulfonic acid, which derivatives can all be prepared from the carboxylic acid by standard procedures and can be reacted with an amine, an alcohol or a mercaptan of the formula $HR^{8'}$ under standard conditions. A carboxylic acid group COOH representing COR^{49} in a compound of the formula **14** can be obtained, for example, from an ester group introduced into the indole system during an indole synthesis by standard hydrolysis procedures.

Compounds of the formula I in which a group COR^8 is an ester group can also be prepared from compounds of the formula **14** in which COR^{49} is a carboxylic acid group by common esterification reactions like, for example, reacting the acid with an alcohol under acid catalysis, or alkylation of a salt of the carboxylic acid with an electrophile like an alkyl halogenide, or by transesterification from another ester. Compounds of the formula I in which a group COR^8 is an amide group can be prepared from amines and compounds of the formula **14** in which COR^{49} is a carboxylic acid group or an ester thereof by common amination reactions. Especially for the preparation of amides the compounds of the formula **14** in which COR^{49} is a carboxylic acid group can be condensed under standard conditions with compounds of the formula $HR^{8'}$ which are amines by means of common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide, carbonyldiazoles like carbonyldiimidazole (CDI) and similar reagents, propylphosphonic anhydride, O-((cyano-(ethoxycarbonyl)-methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU),

diethylphosphoryl cyanide (DEPC) or bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride (BOP-Cl) and many others.

If the residue -Q-R^0 present in an indole of the formula I or the residue R^{50} present in an indole of the formula **14**, or a residue in which functional groups within the residue -Q-R^0 or R^{50} are present in protected form or in the form of a precursor group, have not already been introduced during a preceding step, for example during a synthesis of the indole nucleus, these residues can, for example, be introduced into the 1-position of the indole system by conventional literature procedures well known to one skilled in the art for N-alkylation, reductive amination, N-arylation, N-acylation or N-sulfonylation of ring nitrogen atoms of heterocycles. The starting indole derivative that is to be employed in such a reaction carries a hydrogen atom in the 1-position. N-Alkylation of a ring nitrogen atom can, for example, be performed under standard conditions, preferably in the presence of a base, using an alkylating compound of the formula LG-Q-R^0 or of the formula R^{50}-LG, wherein the atom in the group Q or in the group R^{50} bonded to the group LG in this case is an aliphatic carbon atom of an alkyl moiety and LG is a leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, mesyloxy or trifluormethylsulfonyloxy. LG may, for example, also be a hydroxy group which, in order to achieve the alkylation reaction, is activated by a conventional activating agent. For the preparation of compounds in which A is a direct linkage and an aromatic group is directly bonded to the 1-position of the indole system, conventional arylation procedures can be used. For example aryl fluorides like alkyl fluorobonzoates or 4-fluorophenyl methyl sulfones can be employed as arylating agents. Such processes are described, for example, By S. Stabler, Jahangir, Synth. Commun. 24 (1994) 123; I. Khanna, R. Weier, Y. Yu, X. Xu. F. Koszyk, J. Med. Chem. 40 (1997) 1634. Alternatively a wide variety of substituted aryl iodides, aryl bromides or aryl triflates can serve as arylating agents at the 1-position of the indole system in a copper salt or palladium mediated reaction according to R. Sarges, H. Howard, K. Koe, A. Weissmann, J. Med. Chem, 32 (1989) 437; P. Unangst, D. Connor, R. Stabler, R. Weikert, J. Heterocycl. Chem, 24 (1987) 811; G. Tokmakov, I. Grandberg, Tetrahedron 51 (1995) 2091; D. Old, M. Harris, S. Buchwald, Org. Lett. 2 (2000) 1403, G. Mann, J. Hartwig, M. Driver, C. Fernandez-Rivas, J. Am. Chem. Soc. 120 (1998) 827; J. Hartwig, M. Kawatsura, S. Hauk, K. Shaughnessy, L. J. Org. Chem. 64 (1999) 5575. Moreover such arylations can also be accomplished by reaction of a wide range of substituted aryl boronic acids as demonstrated for example by W. Mederski, M. Lefort, M. Germann, D. Kux, Tetrahedron 55 (1999) 12757.

In the course of the synthesis the employment of microwave assistance for speeding-up, facilitating or enabling reactions may be beneficial or even required in many cases. Some reactions are for example

described by J. L. Krstenansky, I. Cotteril, Curr. Opin. Drug. Disc. & Development., 4(2000), 454; P. Lidstrom, J. Tierney, B. Wathey, J. Westman, Tetrahedron, 57(2001), 9225; M. Larhed, A. Hallberg, Drug Discovery Today, 8 (2001) 406; S. Caddick, Tetrahedron, 51 (1995) 10403.
Preferred methods include, but are not limited to those described in the examples.

The compounds of the present invention are serine protease inhibitors, which inhibit the activity of the blood coagulation enzyme factors Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other proteases whose inhibition is not desired. The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred embodiment of the invention comprises compounds which have a Ki < 1 mM for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same concentration of the inhibitor). The compounds of the invention inhibit factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex.

As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

The present invention also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxis. The present invention also relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances or excipients and/or auxiliary substances or additives.

The invention also relates to the treatment of disease states such as abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee or hip surgery, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, certain viral infections or cancer.
The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis, which can occur following surgery.

The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations, which permit enteral or parenteral administration. The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, cornstarch or derivatives thereof, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 % to 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg.

In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I, and/or

their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I, the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or a physiologically tolerable salt and/or its prodrug, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

When using the compounds of the formula I the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from 0.01 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 50 mg/kg, in particular from 0.1 mg/kg to 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample. Further, a compound of the formula I or its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be labeled with, for example, a radioisotope, and the labeled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

The general synthetic sequences for preparing the compounds useful in the present invention our outlined in the examples given below. Both an explanation of, and the actual procedure for, the various aspects of the present invention are described where appropriate. The following examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the examples can be used to synthesize the compounds of the present invention.

It is understood that changes that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Thus, the following examples are intended to illustrate but not limit the present invention.

Examples

When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tBu group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

Abbreviations used:

As used throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

tert-Butyl	tBu
2,2'-bis(diphenylphoshino-1,1'-binaphthyl	Binap
Bis-(oxo-3-oxazolidinyl)-phosphoryl chloride	BOP-Cl
dibenzylidenacetone	dba
Dicyclohexyl-carbodiimide	DCC
Dichloromethane	DCM

Diethylphosphoryl cyanide	DEPC
4-Dimethyaminopyridine	DMAP
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
Ethyl-diisopropyl-amine	DIPEA
1,1'-Bis(diphenylphosphino)ferrocene	DPPF
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'- tetramethyluronium-Hexafluorophosphate	HATU
N-Bromosuccinimide	NBS
N-Chlorosuccinimide	NCS
N-Iodosuccinimide	NIS
N-Ethylmorpholine	NEM
Methanol	MeOH
Room temperature	RT
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA
O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborate	TOTU

Example 1

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)- 1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 1H-Indole-2,5-dicarboxylic acid 2-ethyl ester 5-isopropyl ester

To a solution of 31 g $AlCl_3$ in 400 ml DCM, 20 ml oxalyl dichloride was added dropwise. Then, after 30 min 20 g 1H-Indole-2-carboxylic acid ethyl ester in 200 ml DCM were added and the reaction mixture was stirred for 2 h. The reaction mixture was poured on to crushed ice and extracted twice with 500 ml DCM. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was taken-up in 500 ml Propan-2-ol and stirred for 4 h at room temperature. After concentration of the reaction mixture under reduced pressure the residue was purified by chromatography on silica gel eluting with an ethyl acetate/heptane 1:10 -> 4:1 gradient.
Yield: 5.24 g.

(ii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 2- ethyl ester 5-isopropyl ester

To a solution of 5.24 g 1H-Indole-2,5-dicarboxylic acid 2-ethyl ester 5-isopropyl ester in 80 ml DMF, 456 mg sodium hydride (60% in mineral oil) were added at RT. After stirring for 30 min 5.3 g 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added and the mixture was stirred for 2 h at RT. Then additional 91 mg sodium hydride (60% in mineral oil) and 1.06 g 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added and stirred for 2 h at RT. After removal of the solvent under reduced pressure the residue was taken-up in DCM (300 ml) and washed twice with water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with heptane/ethyl acetate 6:1. The fractions containing the product were collected and the solvent evaporated under reduced pressure. Yield: 6.3 g.

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 5-isopropyl ester

To a solution of 6.21 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 2- ethyl ester 5-isopropyl ester in 100 ml THF and 40 ml MeOH 52 ml of an aqueous 1M LiOH solution were added and stirred for 2 h. The organic solvents were removed under reduced pressure and the residue acidified with 2 M hydrochloric acid to pH 2. The precipitated product was collected by filtration and dried over P_2O_5 in vacuo to yield a white solid. Yield: 5.77 g.

(iv) (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester

To a solution of 5.0 g Piperidin-4-yl-carbamic acid tert-butyl ester in 15 ml methanol, 7.34 ml acetone, 3.14 g $Na(CN)BH_3$ and 0.3 ml acetic acid were added. After stirring for 16h at room temperature the solvent was removed under reduced pressure and the residue was partitioned between 30 ml of water and 30 ml ethyl acetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give the product as a white solid. Yield: 4.8g. MS (ES^+): m/e= 243.

(v) 1-Isopropyl-piperidin-4-ylamine

To 4.8 g (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 15 ml methanol, 20 ml methanolic hydrochloric acid (8M) were added and the mixture was stirred for 16h. Removal of the

solvent under reduced pressure, followed by removal of residual volatiles by twice coevaporating with toluene, gave the product. Yield: 5.42 g. MS (ES^+): m/e= 143.

(vi) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid isopropyl ester

To a solution of 5.77 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 5- isopropyl ester and 2.79 g 1-Isopropyl-piperidin-4-ylamine hydrochloride in 100 ml DMF, 4.25 g TOTU and 6.6 ml DIPEA were added and the mixture was stirred for 3 h at room temperature. After removal of the solvent under reduced pressure the residue was dissolved in 200 ml ethyl acetate and washed with sat. $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$. After removal of the solvent under reduced pressure the residue was purified by chromatography on silica gel eluting with DCM/MeOH/AcOH/H_2O 95:5:0.5:0.5. The fractions containing the product were collected and the solvent evaporated under reduced pressure. The product was obtained as its acetate salt. Yield: 6.13 g. MS (ES^+): m/e =569, chloro pattern.

(vii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid

To a solution of 6.13 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid isopropyl ester in 200 ml MeOH 54 ml of a 1M aqueous LiOH solution were added and the mixture was heated for 24 h to 60 °C. The reaction mixture was the concentrated under reduced pressure and acidified with 2 M hydrochloric acid to pH 3. Then the mixture was extracted with ethyl acetate (2x200 ml) and the organic layers were dried over $MgSO_4$. After evaporation of the solvent under reduced pressure 5.3 g of the crude acid as a yellow solid was obtained. 600 mg of this acid were purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized after addition of 2M hydrochloric acid to give a white solid. The product was obtained as its hydrochloride. Yield: 280 mg. MS (ES^+): m/e =527, chloro pattern.

(viii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)- 1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 400 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid-hydrochloride and 117 mg 3-hydroxy-azetidine in 15 ml absolute DMF 348 mg TOTU and 558 µl DIPEA were added and the mixture was stirred at RT for 3 h. The solvent was removed in vacuo and the residue purified by chromatography on silica gel using CH_2Cl_2/MeOH/HOAC/H_2O = 9/1/0.1/0.1. The fractions containing the product

were concentrated and purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were concentrated. The residue was dissolved in CH_2Cl_2 and the solution washed with 0.1 N NaOH. The organic phase was dried over Na_2SO_4. After filtration the solvent was removed in vacuo and the residue lyophilized after addition of acetic acid to give a white solid. The product was obtained as its acetate. Yield: 302 mgMS (ES^+): m/e = 582, chloro pattern.

Example 1a

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid

Alternatively 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid can be prepared by the following procedure (a) – (f):

(a) 1H-Indole-2,5-dicarboxylic acid 5-methyl ester

A solution of 25 g 4-Amino-3-iodo-benzoic acid methyl ester, 19 ml 2-Oxo-propionic acid, 30.4 g 1,4-Diaza-bicyclo[2.2.2]octane and 1 g $Pd(OAc)_2$ in 200 ml DMF was heated under argon to 100°C. After 5 h the reaction mixture was concentrated under reduced pressure and the residue was partitioned between 300 ml ethyl acetate and 200 ml 1 M hydrochloric acid. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield a yellow solid (6.4 g). From the aqueous layer additional product slowly precipitated as a white solid (7.9 g) which was collected by filtration. Both fractions were combined, dried in vacuo and used in the next reaction without further purification. Yield: 14.3 g. MS (ES^+): m/e =220.

(b) 1H-Indole-2,5-dicarboxylic acid 2-tert-butyl ester 5-methyl ester

To 13 g 1H-Indole-2,5-dicarboxylic acid 5-methyl ester in 300 ml toluene, 59 ml Di-tert-butoxymethyl-dimethyl-amine were added dropwise at 80°C. Then, the reaction mixture was heated under reflux for additional 6 h. After removal of the solvents under reduced pressure the residue was dissolved in 300 ml DCM and washed with sat. aqueous $NaHCO_3$ solution (2X100 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with a n-heptane/ethyl acetate gradient. The fractions containing the product were collected and concentrated under reduced pressure. Yield: 8.3 g. MS (ES^+): m/e =276.

(c) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 2- tert-butyl ester 5-methyl ester

This compound was prepared using a procedure analogous to that described for the preparation of example 1(ii), using 1H-Indole-2,5-dicarboxylic acid 2-tert-butyl ester 5-methyl ester as the starting material. The compound was chromatographed on silica gel eluting with n-heptane/ethyl acetate 6:1. Yield: 9.6 g. MS (ESI+): m/e = 417, chloro pattern.

(d) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 5-methyl ester

9.5 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 2- tert-butyl ester 5-methyl ester were dissolved in 300 ml trifluoro-acetic acid and stirred for 1 h at RT. Then 200 ml toluene were added and the solvents were removed under reduced pressure. This procedure was repeated three times, then the residue was dried in vacuo. Yield: 8.4 g.

(e) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid methyl ester

This compound was prepared using a procedure analogous to that described for the preparation of example 1 (vi), using 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 5- methyl ester as the starting material. The compound was chromatographed on silica gel eluting with DCM/MeOH/AcOH/H_2O 95:3:0.5:0.5. Yield 10 g. MS (ESI+): m/e = 541, chloro pattern.

(f) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid

To a solution of 8.8 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid methyl ester in 200 ml THF and 100 ml methanol 58.5 ml of a 1 M aqueous LiOH solution were added and the mixture was heated to 70°C for 4 h. After cooling to RT the organic solvents were removed under reduced pressure and the remaining aqueous solution was acidified with half concentrated HCl to pH 2. The precipitated product was collected by filtration. Yield: 7.9 g.

Example 2

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxymethyl-pyrrolidine-1- carbonyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To 50 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid in 1 ml DCM and 0.3 ml NEt_3, 11 mg Pyrrolidin-2-yl-

methanol and 24 mg BOP-Cl were added at RT and the mixture was stirred for 16 h. After removal of the solvent under reduced pressure the residue was directly purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 41 mg. MS (ES^+): m/e=610, chloro pattern.

Example 3

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid 2-oxo-[1,3]dioxolan-4-ylmethyl ester

The title compound was prepared analogously to example 2 with the difference that 4-Hydroxy-methyl-[1,3]dioxolan-2-one was used instead of Pyrrolidin-2-yl-methanol. MS (ES^+): m/e = 627, chloro pattern.

Example 4

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-indole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid methyl ester

To a solution of 500 mg 1H-Indole-2,5-dicarboxylic acid 5-methyl ester and 491 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride in 20 ml absolute DMF, 746 mg TOTU and 1.1 ml DIPEA were added and the mixture was stirred at RT for 2 h. The solvent was removed in vacuo and the residue was directly purified by chromatography on silica gel eluting with a gradient of DCM/MeOH 100%-->60%. The fractions containing the product were combined and the solvent evaporated under reduced pressure. Yield: 0.73 g.

(ii) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid methyl ester

To a solution of 3 g 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid methyl ester in 80 ml absolute DMF 419 mg NaH (60% in mineral oil) were added under an argon atmosphere. After stirring for 30 min. 2.179 g 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide were added and the reaction mixture stirred for 2 h at RT. Then additional 105 mg NaH (60% in mineral oil) and 1.089g 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide were added and the mixture stirred for 1h at RT. The solvent was removed in vacuo and the residue purified by chromatography on silica gel using CH_2Cl_2/MeOH/HOAC/H_2O = 9/1/0.1/0.1. The fractions containing the product were concentrated and lyophilized in a water / CH_3CN mixture. Yield: 3.68 g.

(iii) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid

To a solution of 3.67 g 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-5-carboxylic acid methyl ester in 160 ml CH_2Cl_2, 12.83 ml of a 1M solution of BBr_3 in CH_2Cl_2 were added and the reaction mixture stirred for 1h at RT. After standing for 16 h, additional 12.83 ml of a 1M solution of BBr_3 in CH_2Cl_2 were added and the mixture stirred for 3h at RT. The solvent was removed in vacuo, the residue triturated with diethyl ether and filtrated. The residue was purified by chromatography on silica gel using CH_2Cl_2/MeOH/HOAC/H_2O = 7/3/0.3/0.3. The fractions containing the product were concentrated, triturated with CH_2Cl_2 and the residue was suspended in water and lyophilized. The product was obtained as its hydrobromide. Yield: 2.7 g.

(iv) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 600 mg 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-5-carboxylic acid hydrobromide and 142.6 mg [1,4]Oxazepane in 10 ml absolute DMF, 339 mg TOTU and 541 µl DIPEA were added and the mixture was stirred at RT for 3 h. After standing for 16 h, the solvent was removed in vacuo and the residue purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA) followed by an additional chromatography on silica gel using CH_2Cl_2/MeOH/HOAC/H_2O = 8/2/0.2/0.2. The fractions containing the product were evaporated and lyophilized. The residue was dissolved in CH_2Cl_2. Water was added and the pH of the mixture was adjusted to pH 13 by adding 1N NaOH. The phases were separated and the organic phase dried over Na_2SO_4. After filtration, the solvent was evaporated, the residue dissolved in water and lyophilized after addition of hydrochloric acid. The product was obtained as its hydrochloride. Yield: 481 mg. MS (ES^+): m/e = 581, chloro pattern.

Example 5

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-5-carboxylic acid 1-(2-methoxy-ethoxycarbonyloxy)-ethyl ester

(i) Carbonic acid 1-chloro-ethyl ester 2-methoxy-ethyl ester

To a solution of 11.9 ml 2-Methoxy-ethanol and 17.98 ml 1-chloroethyl-chloroformiate in 200 ml absolute CH_2Cl_2 13.3 ml pyridine were added at 5-10 °C in an argon atmosphere. The mixture was stirred at RT for 5h and washed successively with 1N HCl, with an aqueous solution of $KHSO_4/K_2SO_4$ and water. The organic phase was dried over Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue purified by destillation. Kp. = 88 °C (5.5 mbar). Yield: 22.4 g.

(ii) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-indole-5-carboxylic acid 1-(2-methoxy-ethoxycarbonyloxy)-ethyl ester

To a solution of 700 mg 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-5-carboxylic acid hydrobromide and 883 mg carbonic acid 1-chloro-ethyl ester 2-methoxy-ethyl ester in 20 ml absolute DMF, 1.33 g K_2CO_3 and 803 mg KI were added and the mixture stirred at 60 °C for 16h. After filtration, the solvent was removed in vacuo and the residue purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized. The residue was dissolved in CH_2Cl_2. Water was added and the mixture adjusted to pH 13 by adding 1N NaOH. The phases were separated and the organic phase dried over Na_2SO_4. After filtration, the solvent was evaporated, the residue dissolved in water/CH_3CN and lyophilized after addition of 2 M hydrochloric acid. The product was obtained as its hydrochloride. Yield: 250 mg. MS (ES^+): m/e = 643, chloro pattern.

Example 6

1-[(6-Chloro-pyridin-3-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-indole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 11 with the difference that 2-Bromo-N-(6-chloro-pyridin-3-yl)-acetamide was used instead of 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide in the alkylation step. MS (ES^+): m/e = 581, chloro pattern.

Example 7

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-indole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 4-Bromo-1H-indole-2-carboxylic acid tert-butyl ester

To 7 g 4-Bromo-1H-indole-2-carboxylic acid in 150 ml toluene, 28 ml Di-tert-butoxymethyl-dimethyl-amine were added dropwise at 80°C. The reaction mixture was heated under reflux for additional 12 h. After removal of the solvents under reduced pressure the residue was dissolved in 200 ml DCM and washed with sat. aqueous $NaHCO_3$ solution (2X50 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with n-heptane/ethyl acetate 9:1. The fractions containing the product were collected and concentrated under reduced pressure. Yield: 6.5 g . MS (ESI+): m/e = 297.

(ii) 1H-Indole-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester

To a solution of 7.3 g 4-Bromo-1H-indole-2-carboxylic acid tert-butyl ester in 100 ml DMF, 6.8 ml NEt_3, 276 mg $Pd(OAc)_2$, 128 mg 1,1'-Bis(diphenylphosphino)ferrocene, 12 ml MeOH were added and purged with argon for 15 min. This solution was then purged with carbon monoxide and heated to 70°C for 4 h. The reaction mixture was concentrated under reduced pressure, the residue dissolved in 200 ml DCM and washed with 100 ml water. The organic layer was dried over $MgSO_4$ and, after removal of the solvent under reduced pressure, the residue was purified by chromatography on silica gel eluting with n-heptane/ethyl acetate 9:1. The fractions containing the product were collected and concentrated under reduced pressure. Yield: 3.8 g. MS (ESI+): m/e = 276.

(iii) 1H-Indole-2,4-dicarboxylic acid 4-methyl ester

To a solution of 3.8 g 1H-Indole-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester were dissolved in 100 ml TFA. After 1 h at RT 150 ml toluene were added and the solvents were removed under reduced pressure. The residue was lyophilised after addition of water and acetonitrile. Yield: 2 g.

(iv) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 11 with the difference that 1H-Indole-2,4-dicarboxylic acid 4-methyl ester was used instead of 1H-Indole-2,5-dicarboxylic acid 2-ethyl ester 5-isopropyl ester. MS (ES^+): m/e = 581, chloro pattern.

Example 8

4-(3-Methoxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 3-Methoxy-azetidine and 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-indole-4-carboxylic acid was used instead of Azetidin-3-ol and 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid. MS (ES^+): m/e = 519.

Example 9

4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-indole-4-carboxylic acid was used instead 1-[5-

(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid. MS (ES^+): m/e = 505.

Example 10

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2,5-dicarboxylic acid 5- (isopropoxy-amide) 2-[(1-isopropyl-piperidin-4-yl)-amide]

The title compound was prepared analogously to example 1 with the difference that O-Isopropyl-hydroxylamine hydrochloride was used instead of Azetidin-3-ol. MS (ES^+): m/e = 584, chloro pattern.

Example 11

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H- indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-5-carboxylic acid was used instead of 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid. MS (ES^+): m/e = 553, chloro pattern.

Example 12

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)- 1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound was prepared analogously to example 1 with the difference that 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-4-carboxylic acid was used instead of 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid. MS (ES^+): m/e = 582, chloro pattern.

Example 13

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-4-carboxylic acid 1-(2-methoxy-ethoxycarbonyloxy)-ethyl ester

To a solution of 500 mg 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-4-carboxylic acid in 30 ml DMF 955 mg K_2CO_3, 574 mg KI and 631 mg Carbonic acid 1-chloro-ethyl ester 2-methoxy-ethyl ester were added and the mixture was heated to 60°C for 4 h. After cooling to RT the solvent was removed under reduced pressure and the residue was triturated with DCM. The organic phase was washed with water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC (C18

reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilised. Then the residue was dissolved in CH_2Cl_2. Water was added and the mixture adjusted to pH 13 by adding 1N NaOH. The phases were separated and the organic phase dried over Na_2SO_4. After removal of the solvent the residue was dissolved in water and lyophilised again after addition of 1 M HCl. The product was obtained as its hydrochloride. Yield: 0.293 g . MS (ES^+): m/e = 643, chloro pattern.

Example 14

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-4-carboxylic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester

The title compound was prepared analogously to example 5 with the difference that 4-Chloromethyl-5-methyl-[1,3]dioxol-2-one and 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-4-carboxylic acid was used instead of Carbonic acid 1-chloro-ethyl ester 2-methoxy-ethyl ester and 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-4-carboxylic acid. MS (ES^+): m/e = 639, chloro pattern.

Example 15

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester

The title compound was prepared analogously to example 5 with the difference that 4-Chloromethyl-5-methyl-[1,3]dioxol-2-one and 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-indole-5-carboxylic acid was used instead of Carbonic acid 1-chloro-ethyl ester 2-methoxy-ethyl ester and 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- indole-4-carboxylic acid. MS (ES^+): m/e = 639, chloro pattern.

Experimentals

Pharmacological testing

The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC_{50} value, which was related to the inhibition constant Ki. Purified enzymes were used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis was determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant Ki, the IC_{50} value was corrected for competition with substrate using the formula

$$Ki = IC_{50} / \{1 + (\text{substrate concentration} / Km)\}$$

wherein Km is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973), 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, New York, 100-125; which were incorporated herein by reference).

a) Factor Xa Assay

In the assay for determining the inhibition of factor Xa activity TBS-PEG buffer (50 mM Tris-HCl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN_3) was used. The IC_{50} was determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, Indiana) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.

The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay was initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis was measured by the change in absorbance at 405 nm using a Biotek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The enzyme concentration was 0.5 nM and substrate concentration was 140 µM.

b) Factor VIIa Assay

The inhibitory activity towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 which was incorporated herein by reference). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25 µl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 µl of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM $CaCl_2$, 0.05 % PEG 8000, pH 8.15). Following a 15 minutes preincubation period, the assay was initiated by the addition of 35 µl of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 µM final concentration).

The results are shown in Table 1 for the inhibition of factor Xa, as inhibition constants (Ki).

Table 1

Example	Ki[nM]
1	57
2	113
3	14
4	22
5	9
6	375
7	3
8	133
9	124
10	24
11	8
12	14
13	2
14	1
15	11